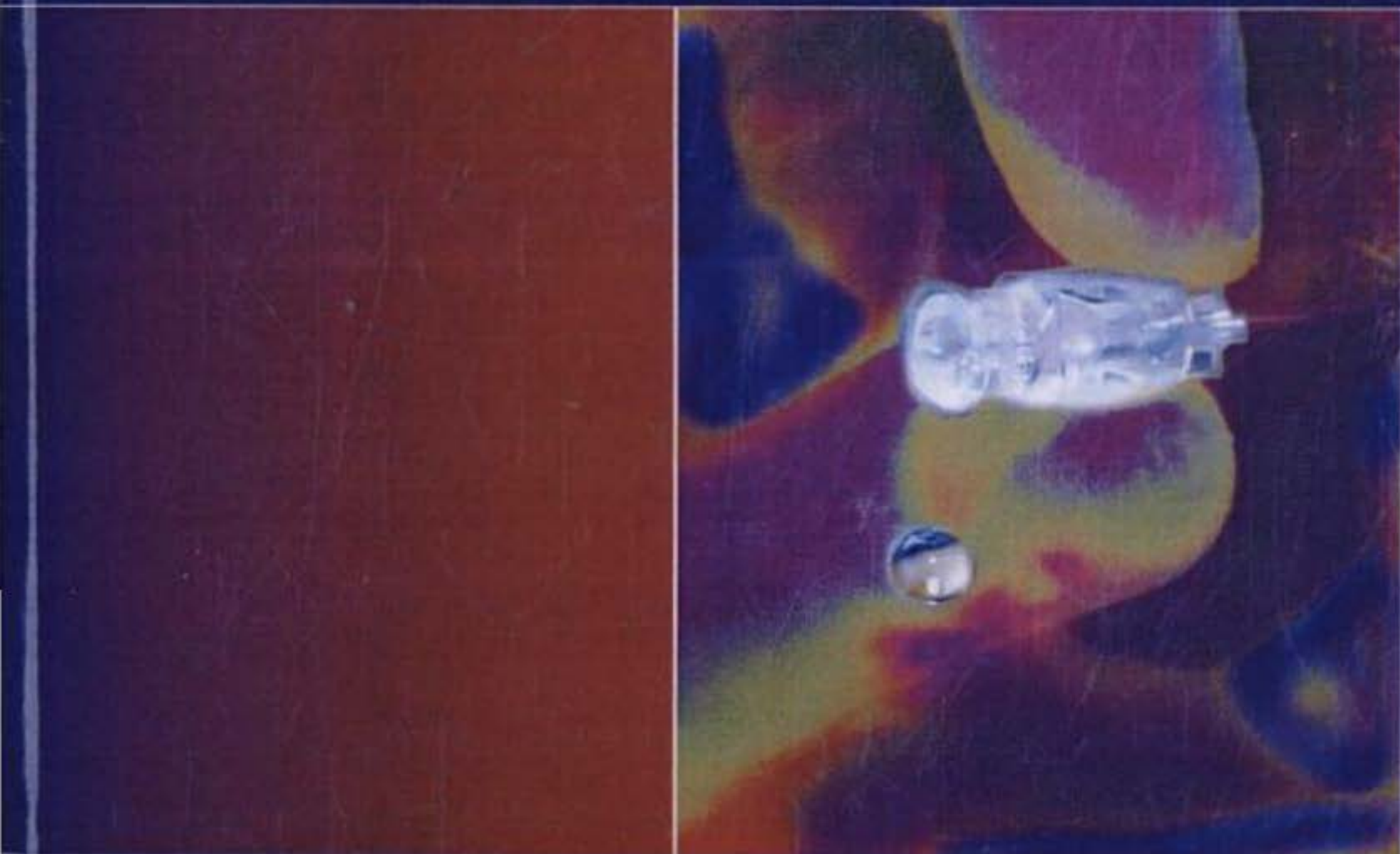


A Practical Guide to
**CANINE AND FELINE
NEUROLOGY**

Edited by
CURTIS W. DEWEY

Illustrated by
Anton G. Hoffman and Carol Rudowsky



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Curtis W. Dewey is staff neurologist at Long Island Veterinary Specialists, Plainview, New York. He received his BS and DVM degrees from Cornell University and his MS degree from the University of Georgia.

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PREFACE

A Practical Guide to Canine and Feline Neurology is an up-to-date, clinically utilizable, small-animal neurology textbook that will appeal to a wide cross section of the veterinary community. It will be particularly helpful to general small-animal practitioners, fourth-year veterinary students, and small-animal interns. It also provides a working knowledge base for residents and specialists. For residents in particular, this book is a valuable asset during preparation for board certification examinations. The extensive reference lists are designed to guide residents and specialists toward more detailed information when needed.

Neuroanatomy is an integral part of clinical small-animal neurology, and is emphasized in this volume. However, attempts have been made to present neuroanatomy in a clinical context. The first chapter is an overview of the basic neuroanatomy needed for accurate localization of lesions. Neuroanatomy is discussed in numerous chapters throughout the text, as well. Because the anatomy of the vestibular system and cerebellum is relatively complex, details of this aspect of neuroanatomy are provided in Chapters 7 and 8, in particular.

The contents are organized in accordance with how a practicing small-animal clinician would likely approach a clinical case. Chapters 1 through 3 are devoted to the “nuts and bolts” of localizing lesions and formulating a diagnostic plan. The bulk of the text is dedicated to descriptions of various disorders. These disorders are organized according to neuroanatomic localization within the framework of the textbook, and according to the DAMNIT scheme (e.g., *D*egenerative, *A*nomalous, *M*etabolic, *N*eoplastic, *I*nflammatory-*I*nfectious-*I*schemic, *T*oxins and *T*rauma) within specific chapters. This organizational scheme allows the clinician to localize a lesion, then immediately consult the appropriate chapter that pertains to that neuroanatomic localization.

The final four chapters, Chapters 15 through 18, deal with subjects that I feel are essential to a comprehensive clinical neurology textbook. Proficiency in nursing care and pain management is an art; it is difficult to achieve, and is learned primarily through experience. Chapters 15 and 16 provide a framework for developing these patient-management skills. Nontraditional therapeutic modalities are rapidly gaining acceptance in modern veterinary practice and deserve a place in clinical textbooks. Chapter 17 presents an overview of complementary and alternative therapies applicable to patients with neurologic disorders. Based on my own experience of performing “emergency literature searches” for various potential neurotoxicities, I have included a chapter dedicated to small-animal neurotoxicity syndromes. Chapter 18 is an excellent resource for neurotoxicities likely to occur in dogs and cats.

I hope that you enjoy using *A Practical Guide to Canine and Feline Neurology*, and find it useful. I welcome your comments regarding helpful revisions; I consider this text to be a work in progress—a necessity due to the dynamic nature of the subject matter.

ACKNOWLEDGMENTS

There are so many people to whom I am thankful, that I can't list them all by name: if I list names, I will surely leave someone out. First and foremost, I want to thank all my family. These are the people who remained confident that I would finish this textbook, even when I wavered. I am very appreciative of my illustrators and contributing authors, without whom this book would not have been completed. I have had the great good fortune to have been trained and inspired by legends of the veterinary profession at Cornell University, the University of Georgia, the University of California-Davis, and Texas A&M University. Their influence on my professional development is reflected in the pages of this book. Similarly, I wish to thank my colleagues for their support and encouragement over the years. In addition, I have had the pleasure of teaching and training excellent students, interns, and residents at Texas A&M University, and Long Island Veterinary Specialists. My ability to effectively impart knowledge to others has been enhanced by my interactions with these people. Finally, I am eternally thankful to the dogs and cats I have treated, and to their loving guardians who entrusted me with their care.

A Practical Guide to
**CANINE AND FELINE
NEUROLOGY**

Chapter 1

FUNCTIONAL AND DYSFUNCTIONAL NEUROANATOMY: THE KEY TO LESION LOCALIZATION

Curtis W. Dewey

I. Introduction

Mastering canine and feline neuroanatomy is a formidable task. The complexity of the subject matter often discourages the veterinary student, as well as the clinician, from becoming proficient in clinical neurology. Although understanding clinical neurology depends upon a working knowledge of neuroanatomy, an intricate knowledge of neuroanatomy is not necessary. This chapter reviews the basic functional and dysfunctional neuroanatomy necessary to understand the neurologic examination (discussed in Chapter 2) and to interpret clinical signs of neurologic dysfunction. Normal functions of specific areas of the nervous system, as well as clinical signs of dysfunction, are described concurrently.

II. The Brain

The brain includes the cerebrum, the brain stem, and the cerebellum. The brain stem includes the diencephalon (thalamus, hypothalamus), the midbrain (mesencephalon), the pons (ventral metencephalon), and the medulla oblongata (myelencephalon). Although the diencephalon is technically the rostral-most aspect of the brain stem, it is functionally (and dysfunctionally) more similar to the cerebrum than the remainder of the brain stem (midbrain through medulla). In this text, the term "forebrain" will be used to describe the combination of cerebrum and diencephalon. The cerebellum (dorsal metencephalon) is the final brain subdivision and will be discussed in more detail in Chapter 8. The upper motor neurons originate from various regions of the brain. The term "upper motor neuron" (UMN) refers to the neurons of the brain that control motor activity of the body. The UMNs exert their effects by stimulating or inhibiting the neurons that directly innervate the muscles. The actual neurons that innervate the muscles are lower motor neurons (LMNs). In other words, the UMN "tells" the LMN what to do (Fig. 1.1). The UMN system is responsible for (1) initiation of voluntary movement, (2) maintenance of muscle tone for support against gravity, and (3) the regulation of posture. The UMN system is often divided into pyramidal (mainly located in the motor area of the cerebral cortex) and extrapyramidal (mainly located in the brain-stem nuclei) neurons. In primates, the pyramidal system plays a very important role in control over the LMN and thus voluntary motor activity, whereas the extrapyramidal system is the predominant UMN system in dogs and cats. Gait is generated in the brain stem of dogs and cats. The exact location of the brain-stem center for gait generation in dogs and cats is unknown, but the midbrain is thought to play a major role.

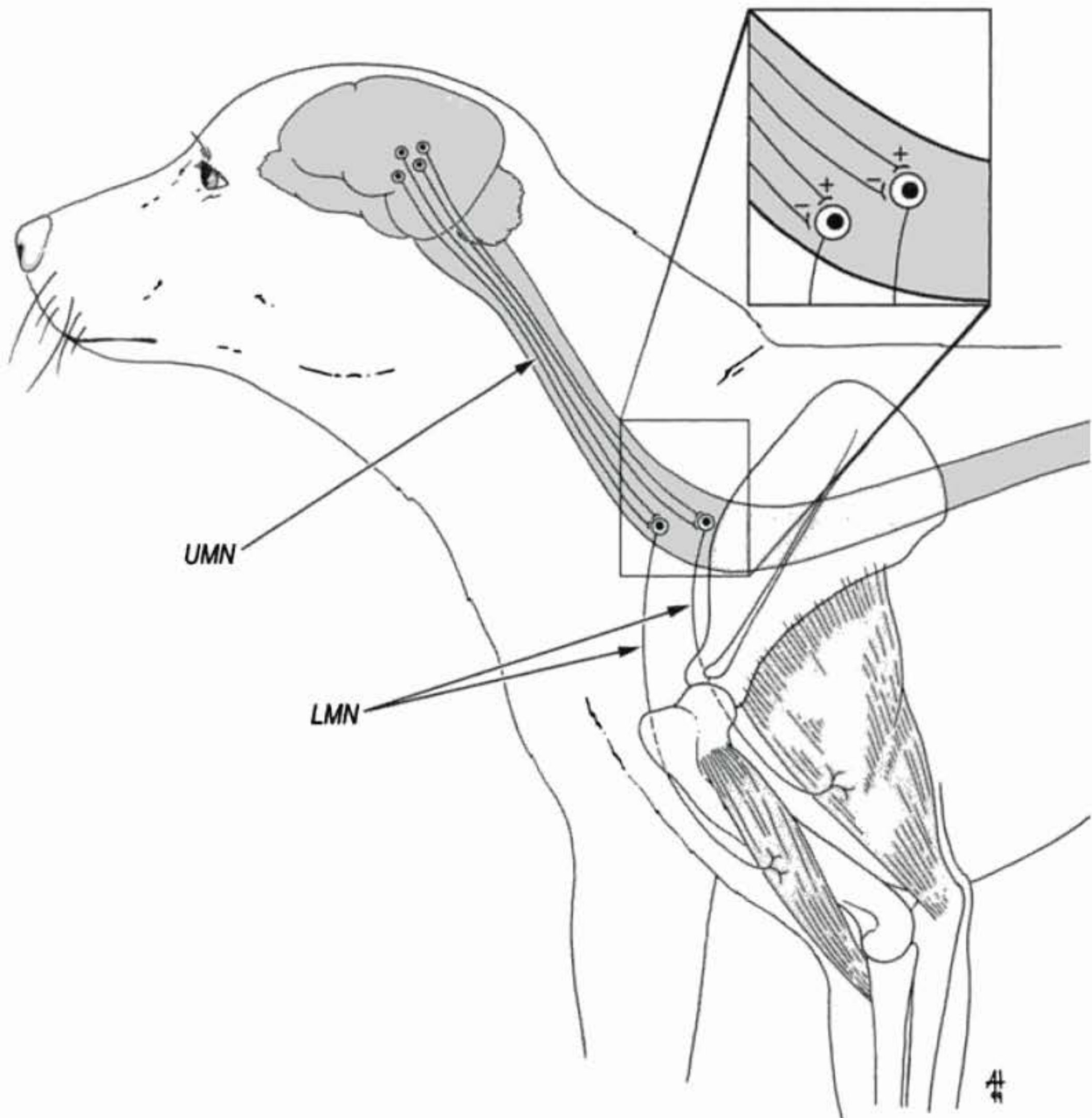


Fig. 1.1. Schematic representation of the association between the upper motor neuron (UMN) and the lower motor neuron (LMN)(Illustration by Anton Hoffman).

- A. Cerebrum (Fig. 1.2; see Table 1.1 for clinical signs of forebrain dysfunction)^{1-3,5,6,8-10}
1. The descending tracts to the limbs (corticospinal tracts) are mainly contralateral. Similarly, cerebral cortical influence over cranial nerve nuclei (corticonuclear tracts) is predominantly contralateral. These cerebral cortical tracts are of minor importance in dogs and cats, in comparison with humans. However, damage to cerebral cortical neurons or their associated white matter tracts may result in subtle, contralateral hemiparesis.
 2. Conscious proprioception (position sense), tactile sensation, and some nociception (face) are represented in the contralateral cerebral hemisphere. Conscious proprioception refers to position sense as perceived at the cerebral level. The

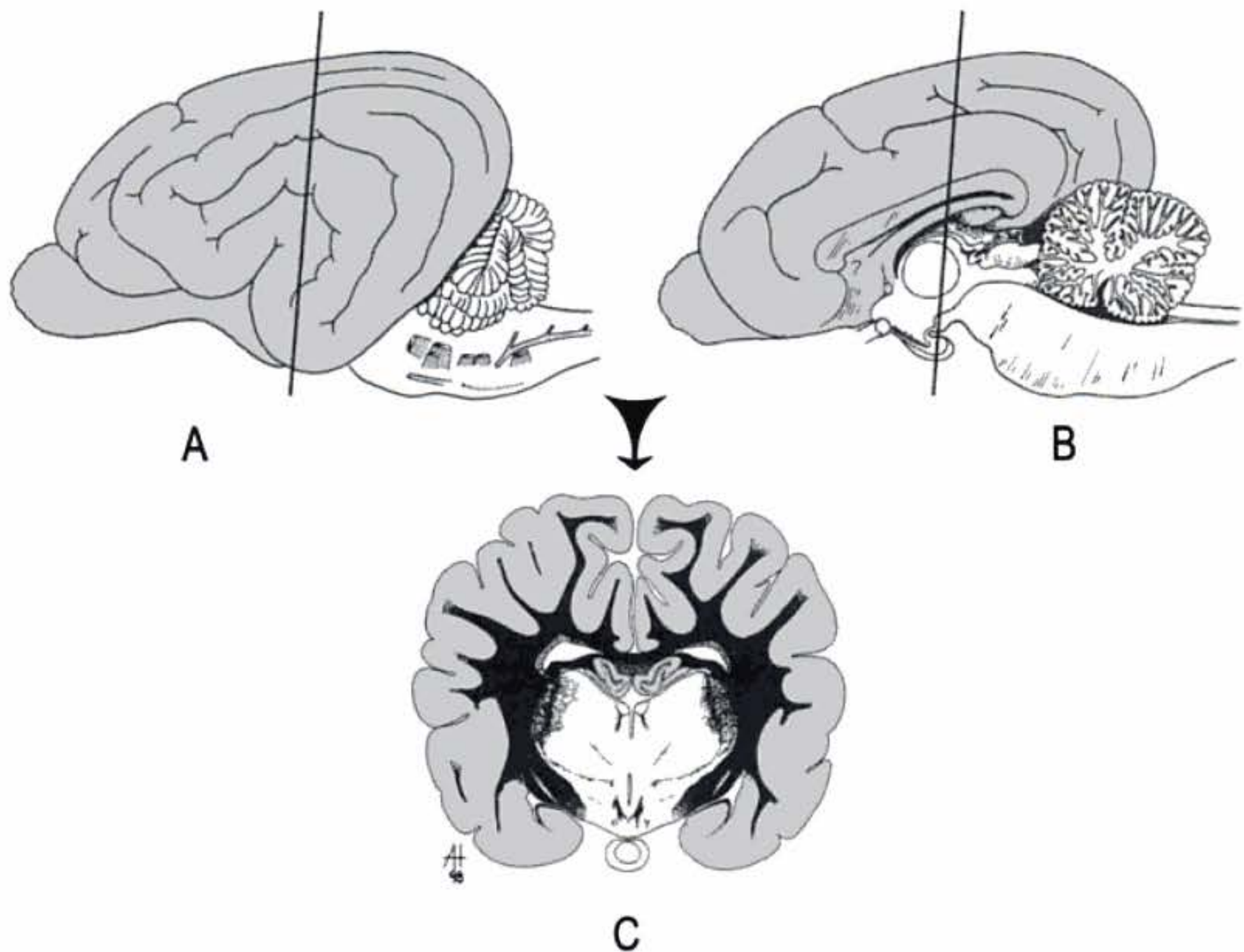


Fig. 1.2. The cerebrum (shaded), depicted in (A) lateral, (B) sagittal, and (C) cross-sectional (axial) views (Illustration by Anton Hoffman).

- modality of conscious proprioception is conveyed to the cerebrum primarily via the dorsal column/medial lemniscus pathways (e.g., fasciculus cuneatus for thoracic limb, spinomedullary tract for pelvic limb) and is best evaluated with the animal in a standing position (i.e., proprioceptive positioning—see Chapter 2).
3. The combination of conscious proprioceptive deficits (usually contralateral to a cerebral lesion) with a normal or near-normal gait is a hallmark of cerebral dysfunction.
 4. Lesions of the cerebrum often cause behavior change, altered mental status (e.g., obtundation), seizure activity, walking in wide circles (usually in the direction of the lesion), head-pressing, and menace deficits. The deficits in the menace response are primarily contralateral. Contralateral deficits of facial sensation may also be appreciated (see note in discussion of the pons).
 5. Patients with structural disease (e.g., tumors) of the cerebrum, or any area of the brain, may exhibit neck pain. This phenomenon is thought to be due to factors such as meningeal stretching and referred pain. It is important that the clinician realize that structural brain disease can cause neck pain, and that this

Table 1.1: Neurologic Signs of Forebrain Dysfunction

Evaluations	Clinical signs
Mental status	Normal, obtunded, demented, stupor (less likely)
Behavior	Normal, hemi-inattention, wandering, vocalizing, dull
Seizures	Present or absent
Posture	Normal, ipsilateral head turn (yaw), horizontal neck carriage, head-pressing
Gait	Normal, ataxic, ipsilateral circling (usually wide), movements with lack of purpose
Cranial nerve evaluation	Normal, contralateral perceptual deficits (i.e., menace response, facial sensation)
Postural reactions/voluntary motor abilities	Contralateral postural reaction deficits; +/- mild contralateral hemiparesis
Spinal reflexes	Intact
Spinal hyperesthesia	Present or absent, especially in the cervical spine
Pain perception	Usually normal; may see mild contralateral sensory loss
Micturition	May show inappropriate urination

Source: Courtesy of Dr. Joan Coates.

clinical finding does not necessarily indicate multifocal or diffuse disease (i.e., another lesion in the cervical spinal cord area). Structural lesions of the forebrain area (cerebrum, diencephalon) appear more likely to result in neck pain than lesions of the caudal brain stem.

6. "Hemi-inattention syndrome," or "hemineglect syndrome," refers to a phenomenon in which a patient with a structural forebrain lesion ignores input from one-half of his or her environment. Since most sensory stimuli are interpreted primarily in the cerebral hemisphere contralateral to the stimulus side, the side that the patient ignores is contralateral to the side of the lesion. These patients may eat from only one-half of the food bowl, turn the opposite direction when called by name (i.e., when called from the ignored side), and ignore or have difficulty localizing nociceptive (e.g., skin pinch) stimuli when applied contralateral to the side of the brain lesion.

Note: Patients with structural lesions of the cerebrum occasionally exhibit anisocoria, which may be subtle. They may also exhibit mild facial muscle paresis, often demonstrated best by observing asymmetry of the lip commissures with the patient's nose held in a vertical position. The cerebral cortex normally has a facilitatory influence over the contralateral facial nucleus and an inhibitory influence over the contralateral parasympathetic oculomotor nucleus. Therefore, a unilateral cerebral lesion may cause contralateral miosis (disinhibition of the oculomotor nucleus), and contralateral facial paresis.

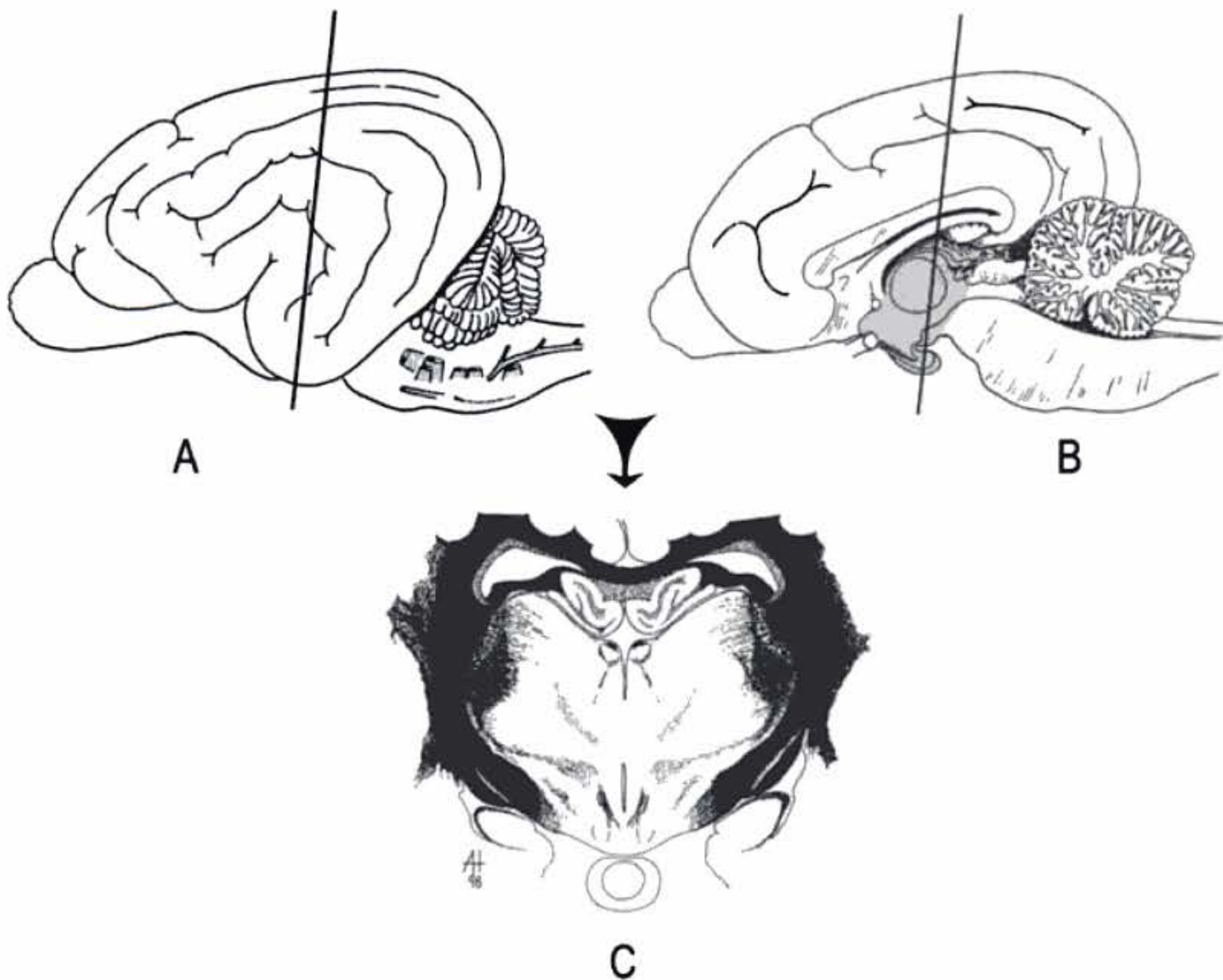


Fig. 1.3. The diencephalon, depicted in (A) lateral (covered by the cerebrum), (B) sagittal (shaded), and (C) cross-sectional (axial) views (Illustration by Anton Hoffman).

B. Diencephalon (Fig. 1.3)^{1,2,4,6,11}

1. Signs of dysfunction are often similar to those associated with cerebral disease. In fact, all of the clinical signs of dysfunction listed above for cerebral disease may be observed in patients with diencephalic disease (see Table 1.1).
2. Patients with diencephalic dysfunction may also exhibit evidence of endocrine dysfunction (e.g., PU/PD), abnormal eating patterns, and problems with temperature regulation. Uncommonly, animals with diencephalic disease act non-specifically painful (thalamic syndrome). Absence of these signs does not rule out a diencephalic lesion, however.
3. The optic nerves or their relays with lateral geniculate nuclei may be affected, resulting in visual impairment and deficient menace responses.
4. Large lesions of the diencephalon may produce stupor and coma as the diencephalon is part of the ascending reticular activating system (ARAS) projecting to the cerebral cortex. The ARAS is responsible for maintaining the awake state in normal animals.

Note: The sensory modality of vision (Fig. 1.4) is carried by the optic nerves (CN II), which are associated with the forebrain (cerebrum and diencephalon). Axons of the optic nerve arise from the ganglion neurons of the retina. The majority of axons in each optic nerve carrying visual information for cerebral cortical recognition cross to the opposite side at the level of the optic chiasm (65% crossing in the cat, 75% in the dog). These axons then synapse on neurons in the lateral geniculate nucleus (LGN) of the diencephalon. These LGN neurons, in turn, relay information to the occipital area of the cerebral cortex for the perception of sight. Focal lesions of the diencephalon and/or cerebrum may result in menace response deficits that are primarily contralateral to the lesion. It is important to note that the menace response involves cerebral cortical integration and interpretation, and therefore is **not** a reflex. The pupillary light reflex (PLR) involves optic nerve axons not destined for cerebral cortical recognition and is discussed in the following section (II.C) concerning the midbrain.

C. Midbrain (Fig. 1.5; see Table 1.2 for clinical signs of brain-stem [caudal to the diencephalon] dysfunction)^{1-6,12-15}

1. Lesions from the midbrain through the medulla are more likely to produce severe disturbances of consciousness (stupor, coma) due to impairment of the ARAS.
2. Lesions from the midbrain through the medulla typically cause obvious gait abnormalities (UMN paresis or plegia). These can be unilateral or bilateral, depending on the size of the lesion. On each side of the midbrain, ventrolateral to the mesencephalic aqueduct, is a collection of neurons called the red nucleus. Each red nucleus gives rise to axons that cross the midline and become the rubrospinal tract. The rubrospinal tracts are thought to be important in gait generation in dogs and cats. If the midbrain lesion is focal enough (unlikely due to the small size of the midbrain), an ipsilateral (caudal midbrain) or contralateral (rostral midbrain) hemiparesis with postural reaction deficits may predominate. *The anatomic landmark for focal lesions that will produce ipsilateral gait and postural reaction deficits appears to be in the vicinity of the caudal midbrain and rostral pons.* Lesions rostral to the midbrain cause contralateral postural reaction deficits and mild or inapparent contralateral paresis. Midbrain lesions seen in clinical practice are usually large enough that the signs are bilateral and severe (e.g., decerebrate rigidity in brainstem herniation).
3. The oculomotor nuclei (motor to extraocular muscles and parasympathetic to pupil) and trochlear nuclei are located in the midbrain. Axons from these nuclei comprise cranial nerves (CN) III and IV, respectively. Cranial nerves III and IV traverse the cavernous sinus at the base of the brain. Other cranial nerves that pass through this sinus include the ophthalmic and maxillary branches of CN V (from the pons) and CN VI (from the medulla). *Cavernous sinus syndrome* refers to dysfunction of more than one of these aforementioned cranial nerves.

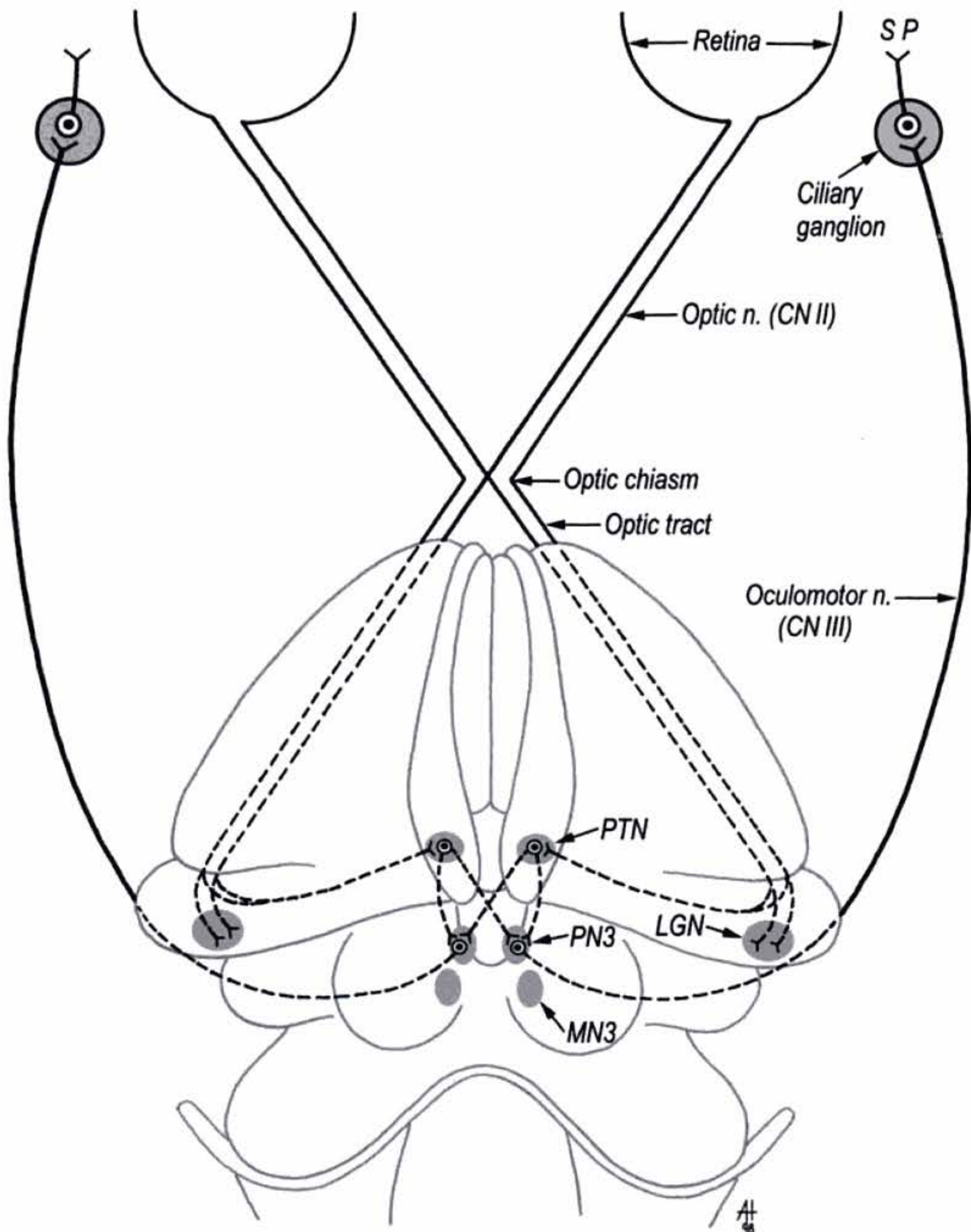


Fig. 1.4. Neuroanatomic pathways for vision and pupillary constriction. LGN, lateral geniculate nucleus; PTN, pretectal nucleus; PN3, parasympathetic nucleus of cranial nerve III; MN3, motor nucleus of cranial nerve III; SP, sphincter pupillae muscle (Illustration by Anton Hoffman).

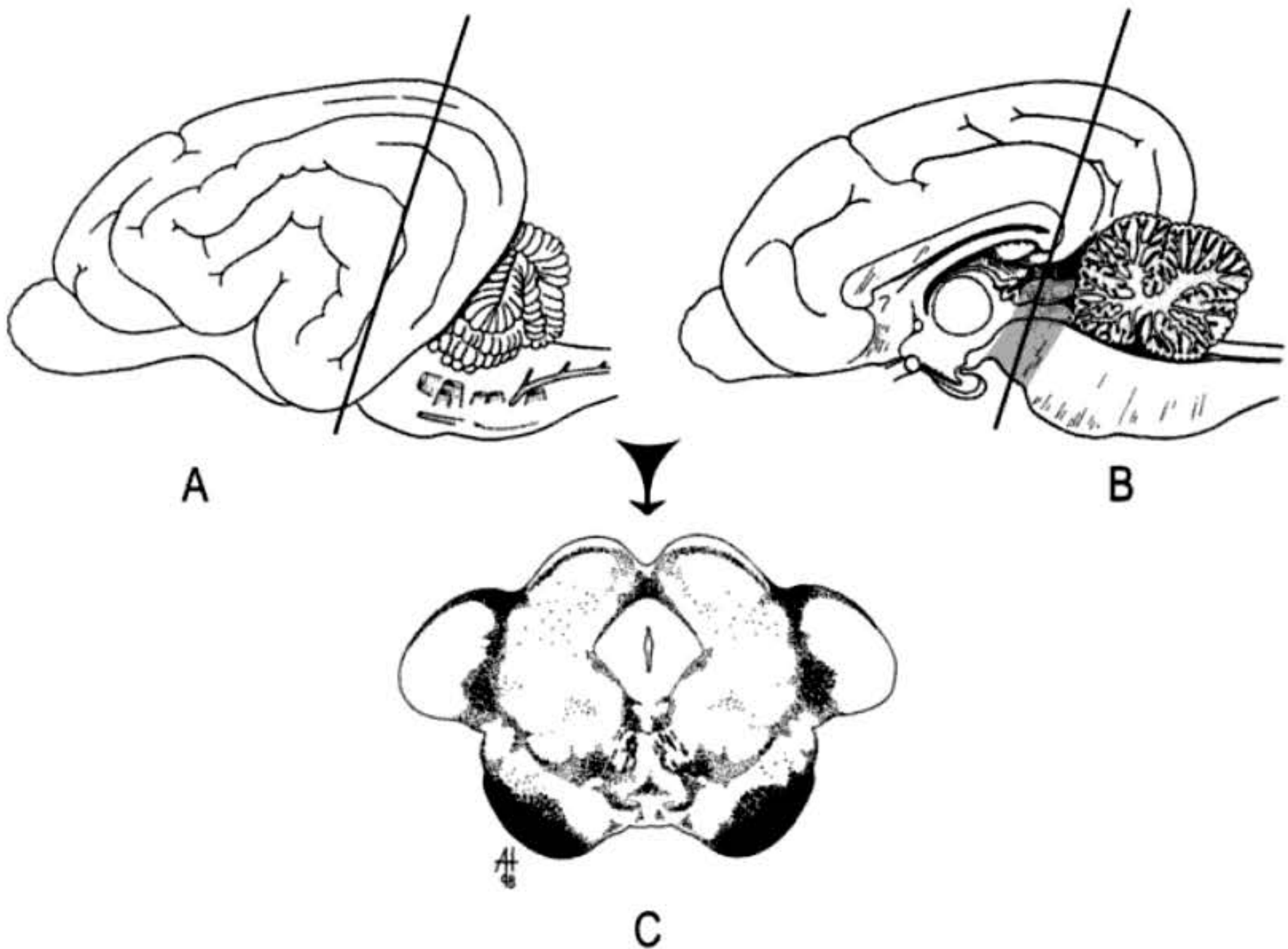


Fig. 1.5. The mesencephalon (midbrain), depicted in (A) lateral (covered by the cerebrum), (B) sagittal (shaded), and (C) cross-sectional (axial) views (Illustration by Anton Hoffman).

4. The origin of the tectotegmentospinal tract (sympathetic innervation of the eye) is in the midbrain. The diencephalon has influence over this part of the midbrain.

Note: Axons of CN II that are involved in reflex activity (rather than cerebral cortical recognition) do not synapse at the level of the LGN of the diencephalon (Fig. 1.4). Those axons involved in the PLR bypass the LGN and synapse on neurons in the pretectal nuclei (PTN). These nuclei are located in the transition zone between diencephalon and midbrain. The majority of the axons from each PTN will cross to the opposite side and synapse on neurons of the parasympathetic oculomotor nucleus (CN III). These latter neurons give rise to the parasympathetic portion of the oculomotor nerve, which mediates pupillary constriction. Since there are two levels of crossing in

Table 1.2: Neurologic Signs of Brain-Stem Dysfunction (Midbrain through Medulla)

Evaluations	Clinical signs
Mental status	Normal, obtunded, stupor, coma
Posture	Normal, head tilt (ipsilateral/contralateral), wide-base stance; recumbent patients may manifest decerebrate or decerebellate rigidity
Gait	Normal, mild-severe ipsilateral tetraparesis/hemiparesis, mild dysmetria, spastic
Cranial nerve evaluation	Ipsilateral deficits; CN III–XII may be affected depending upon lesion extent; ipsilateral or bilateral Horner's syndrome
Postural reactions/voluntary motor ability	Mild-severe ipsilateral deficits
Spinal reflexes	Intact; may have ipsilateral hyperreflexia
Spinal hyperesthesia	Present (inflammatory disorders) or absent
Pain perception	Usually intact; dependent upon mental status
Micturition	Usually intact; severe lesions may manifest absent micturition reflex

Source: Courtesy of Dr. Joan Coates.

this pathway (chiasm level and pretectal level), the direct PLR (pupillary constriction on the side in which the light is shone) tends to be a bit stronger than the indirect (pupillary constriction on the opposite side in which the light is shone). The other reflex pathway for CN II axons also involves the midbrain. Some of the axons that bypass the LGN will synapse on neurons in the rostral colliculus, located in the roof (tectum) of the midbrain. These neurons project to various areas of the brain stem to mediate reflex movements of the eyes, neck, head, and limbs in response to visual stimuli.

D. Pons (Fig. 1.6)^{1–4,7,8,12,13,16,17}

1. The motor nucleus of CN V (trigeminal nerve) is located here. The sensory nuclei and tract of CN V are located from the midbrain to the cranial cervical spinal cord.
2. Lesions of the pons typically cause severe disturbances of consciousness and UMN paresis/plegia. Axons from the reticular formation of the pons give rise to the pontine reticulospinal tracts.
3. The major respiratory centers are located in the pons and medulla (mainly), so abnormal respiratory activity may be apparent with damage to the pons.

Note: Sensory information from the face (Fig. 1.7) travels to the brain via branches of the trigeminal nerve (CN V). The cell bodies (first-order neurons) of these afferent nerves are located in the trigeminal ganglion within the petrous temporal bone of the skull. Once these axons traverse the trigeminal canal of the petrous temporal bone to reach the brain stem, they form the sensory tract of CN V, which extends from the mid-brain level through the remainder of the brain stem, to reach the most cranial aspect of the cervical spinal cord. Medial to the spinal tract of CN V is the nucleus of the spinal tract of CN V. The axons of the spinal tract of CN V synapse somatotopically on this nucleus. The neurons from this nucleus (second-order neurons) project axons to neurons of the contralateral thalamus (quintothalamic tract). These thalamic third-order neurons then project axons to the cerebral cortex for conscious recognition. Brain stem lesions caudal to the diencephalon therefore may lead to ipsilateral deficits in facial sensation, whereas forebrain lesions produce contralateral deficits.

E. Medulla (Fig. 1.8)^{1-4,12,13,16-20}

1. The nuclei of CN VI (abducent nerve), VII (facial nerve), IX (glossopharyngeal nerve), X (vagus nerve), XI (accessory nerve), and XII (hypoglossal nerve) are located in the medulla, so dysfunction of one or more of these cranial nerves (discussed in Chapter 2) may be evident.
2. This is also the location of the vestibular nuclei (rostral, medial, caudal, lateral). The functional neuroanatomy associated with the vestibular system is discussed in more detail in Chapter 7.
3. Lesions of the medulla can cause alterations of consciousness, respiratory disturbance, and autonomic dysfunction (heart rate and blood pressure).
4. Axons from the medullary reticular formation give rise to the medullary reticulospinal tracts. Damage to the medulla often results in UMN paresis/plegia from interference with these and other UMN tracts from the brain stem.
5. Abnormal respiration is possible, since the major respiratory centers are located in the medulla. The neurons of the medullary respiratory centers can be thought of as the UMNs of respiration, which send axons to the LMNs. The LMNs for respiration are located in the grey matter of the caudal cervical (C₅C₆C₇-phrenic nerve) and thoracic (intercostal nerves) spinal cord segments.

Note: Connections between the extraocular nuclei (III, IV, VI) and vestibular input (VIII) are essential for appropriate ocular movements when the head is moved. The connections are maintained by a tract in the brain stem called the *medial longitudinal fasciculus (MLF)*.

F. Cerebellum (see more in Chapter 8)^{1-4,16,21-23}

1. The cerebellum does **not** initiate movement. It coordinates and regulates the rate and range of movement by acting as a comparator. Lesions here tend to cause exaggerated movements (e.g., hypermetria).

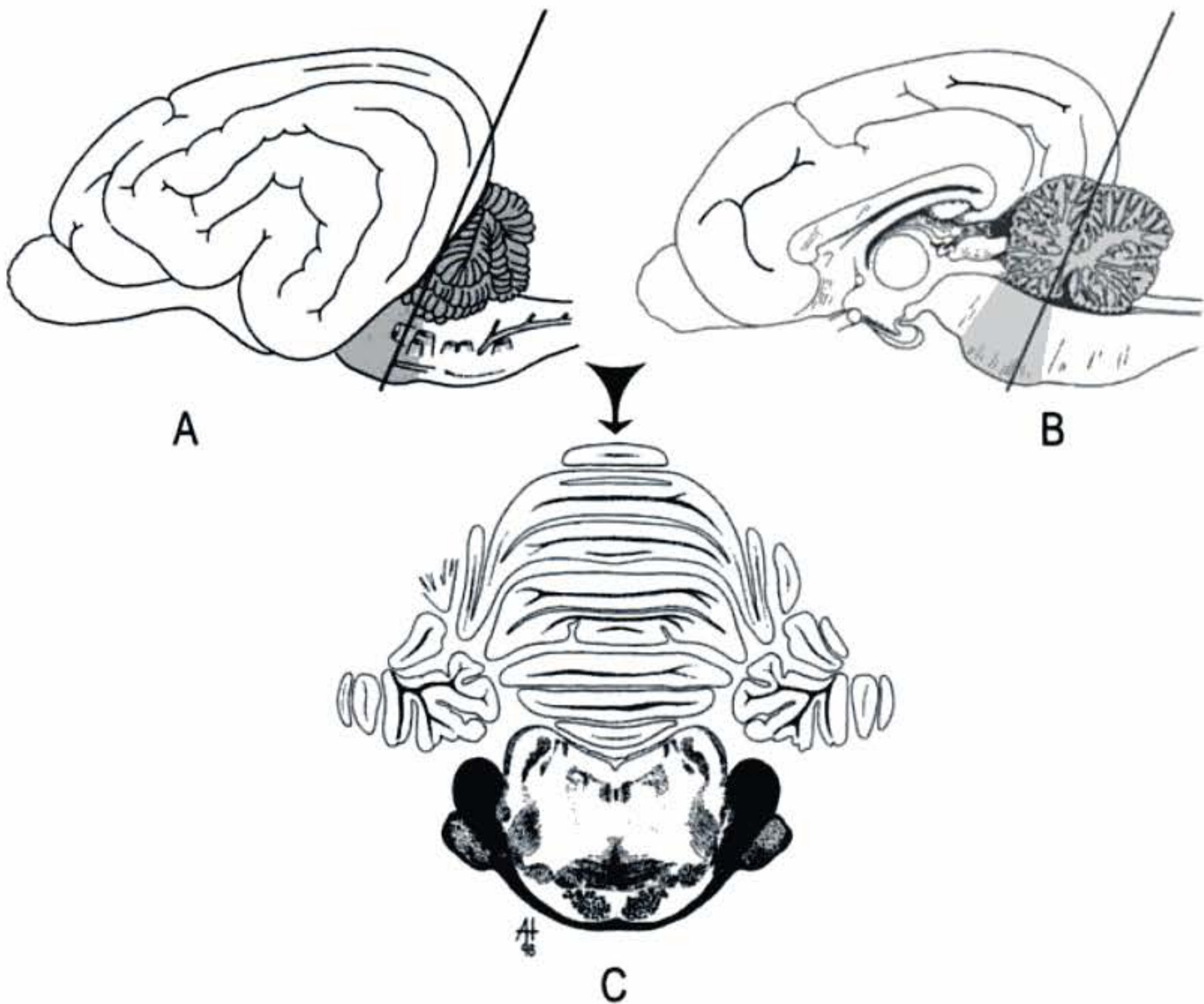


Fig. 1.6. The ventral metencephalon (pons), depicted in (A) lateral (shaded), (B) sagittal (shaded), and (C) cross-sectional (axial) views (Illustration by Anton Hoffman).

2. Lesions of the cerebellum can cause ataxia (unconscious proprioceptive loss) without paresis.
3. Intention tremors, which are tremors initiated by a voluntary movement (e.g., reaching for a treat) may occur, and are often most notable in the head region.
4. There are direct connections of the cerebellum with the vestibular system, so evidence of vestibular dysfunction may accompany cerebellar disease.
5. Lesions of the cerebellum can cause menace deficits with normal vision. The anatomic pathway responsible for this phenomenon is unknown.

III. The Spinal Cord^{1,4,5,8,24–28}

With the exception of the first one or two cervical segments, and a few segments at the thoracolumbar junction level, most spinal cord segments are positioned cranial

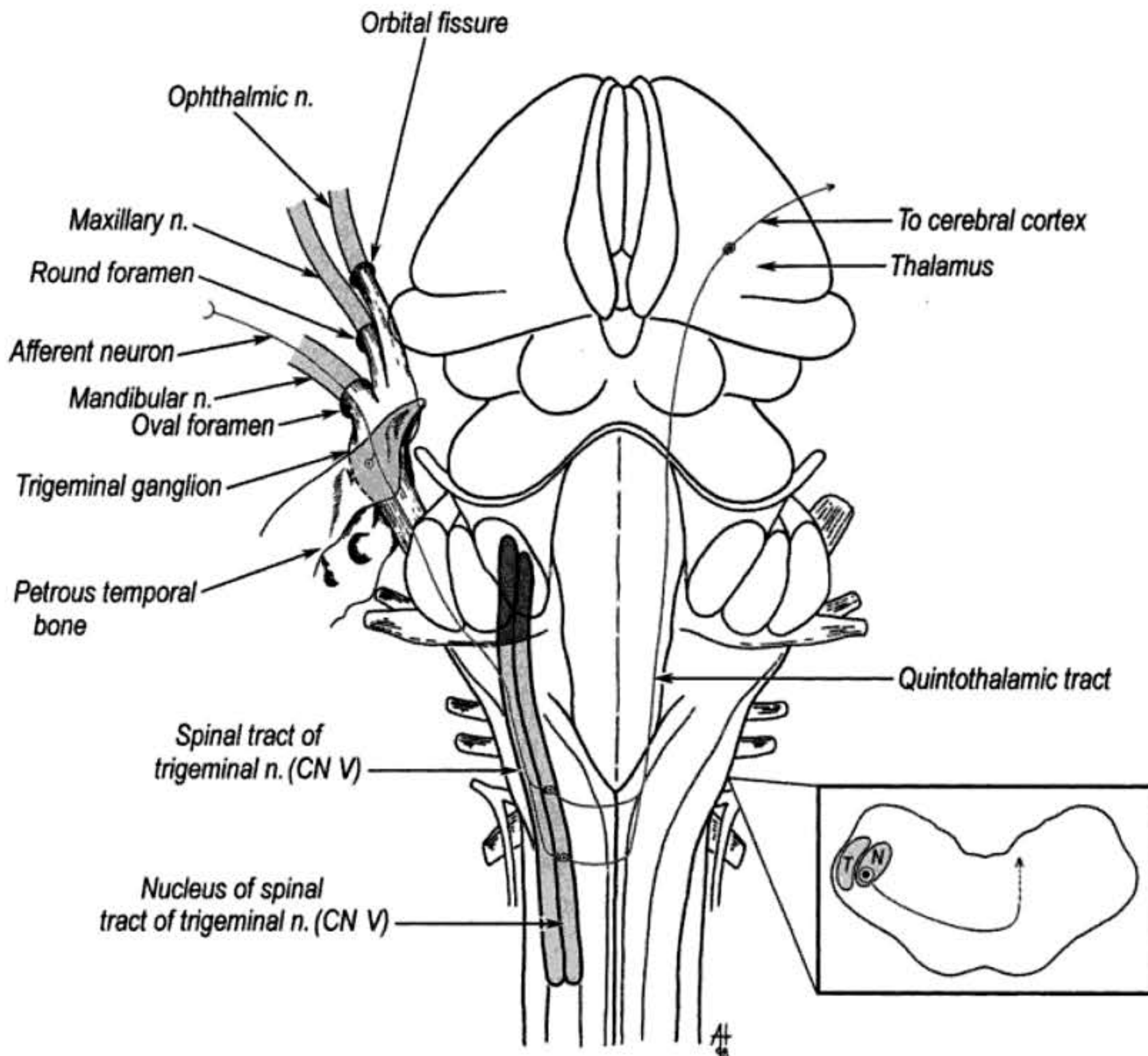


Fig. 1.7. Neuroanatomic pathway for facial sensation. T, spinal tract of cranial nerve V; N, nucleus of spinal tract of cranial nerve V. The inset represents a cross-sectional view of T and N at the indicated level (Illustration by Anton Hoffman).

in the vertebral canal relative to the vertebra of the same number (Fig. 1.9). In medium- to large-breed dogs, the spinal cord terminates at the L6–L7 vertebral level. In small-breed dogs this spatial relationship is shifted caudally by one-half to one vertebral segment. The termination of the spinal cord in cats is usually over the body of S1.

The spinal cord white matter is conceptually divided into dorsal, lateral, and ventral funiculi (Fig. 1.10). The axons or tracts of brain UMNs descend through the spinal cord, synapsing on lower motor neurons of the spinal cord grey matter. The UMN tracts, mainly facilitory to limb flexor muscles and inhibitory to extensors, are located in lateral funiculi of the cord (corticospinal, rubrospinal, medullary reticulospinal). Those facilitory to limb extensors and inhibitory to flexors are located in

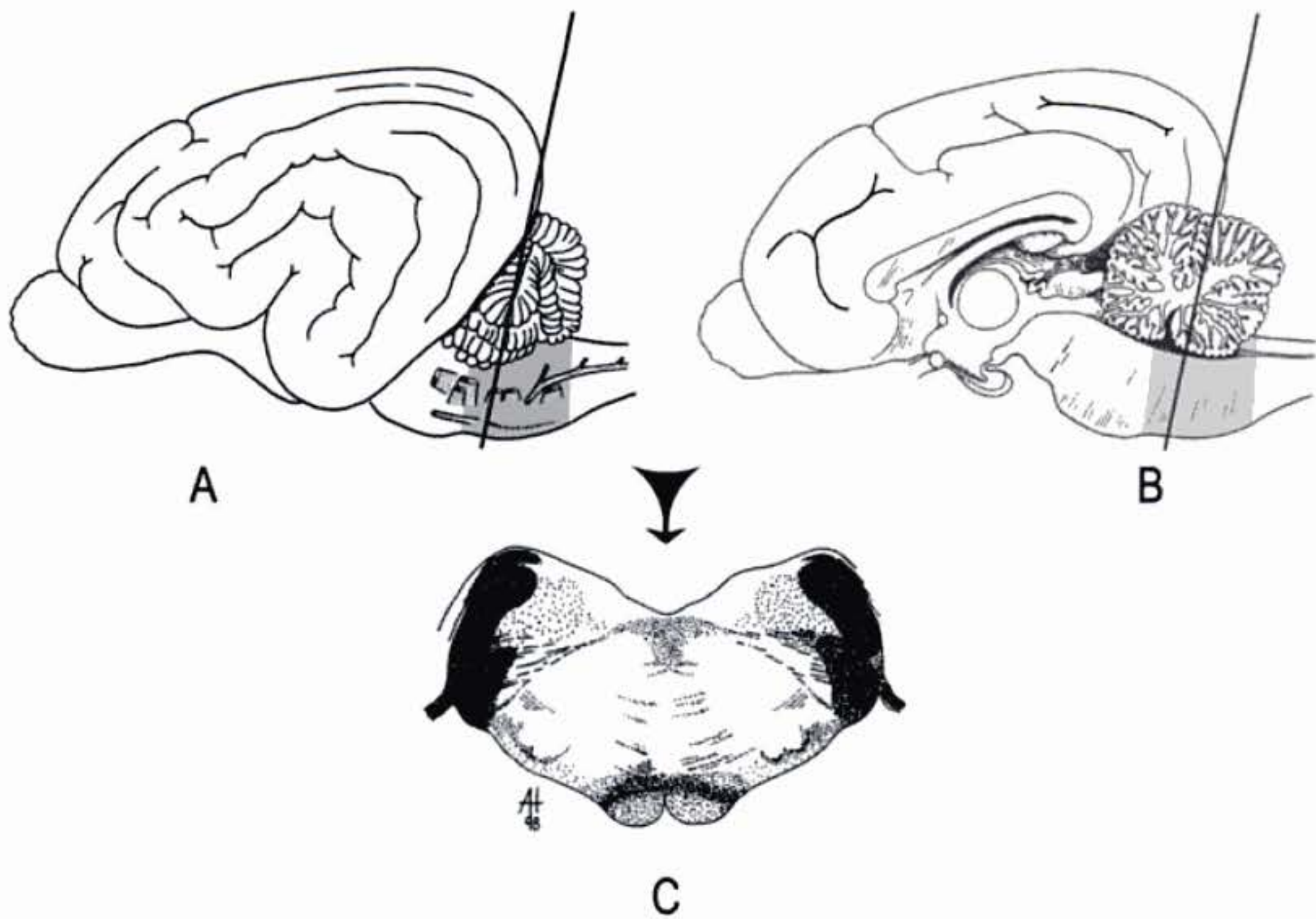


Fig. 1.8. The myelencephalon (medulla), depicted in (A) lateral (shaded), (B) sagittal (shaded), and (C) cross-sectional (axial) views (Illustration by Anton Hoffman).

the ventral funiculus (pontine reticulospinal, vestibulospinal). Ascending sensory tracts for proprioception (spinocerebellar tracts, spinomedullary tract, fasciculus cuneatus and gracilis) and nociception (spinothalamic tract, spinocervicothalamic tract) are located mainly in the dorsal and lateral funiculi (Fig. 1.11). Interference of the UMN influence over the LMN (i.e., the upper motor neuron lesion) typically results in a “release” of muscle inhibition (disinhibition), usually more apparent in the extensor muscles. The result is paresis with normal to increased reflex activity and increased extensor muscle tone. Occasionally, a patient is encountered with decreased muscle tone (hypotonia) and intact reflexes; this may represent a relatively greater disturbance to UMN facilitory pathways versus inhibitory pathways. The reflex activity is at least normal if not hyperactive because the reflex arc is not affected by the UMN lesion. Sensory pathways travel cranially up the spinal cord to the brain mainly in dorsal and lateral funiculi. Conscious proprioception is represented in the contralateral cerebral cortex, and unconscious proprioception (spinocerebellar tracts) is mainly ipsilateral. Pain sensation is functionally bilateral. Although the terminal spinal cord segments are technically part of the spinal cord, they also supply the nerve roots of the cauda equina. In this text, the cauda equina will be defined as the nerve roots derived from the cord segments L7 and caudally.

It is of **vital importance** to understand that pain perception means cerebral cortical recognition and response to a noxious stimulus. The withdrawal reflex is not pain

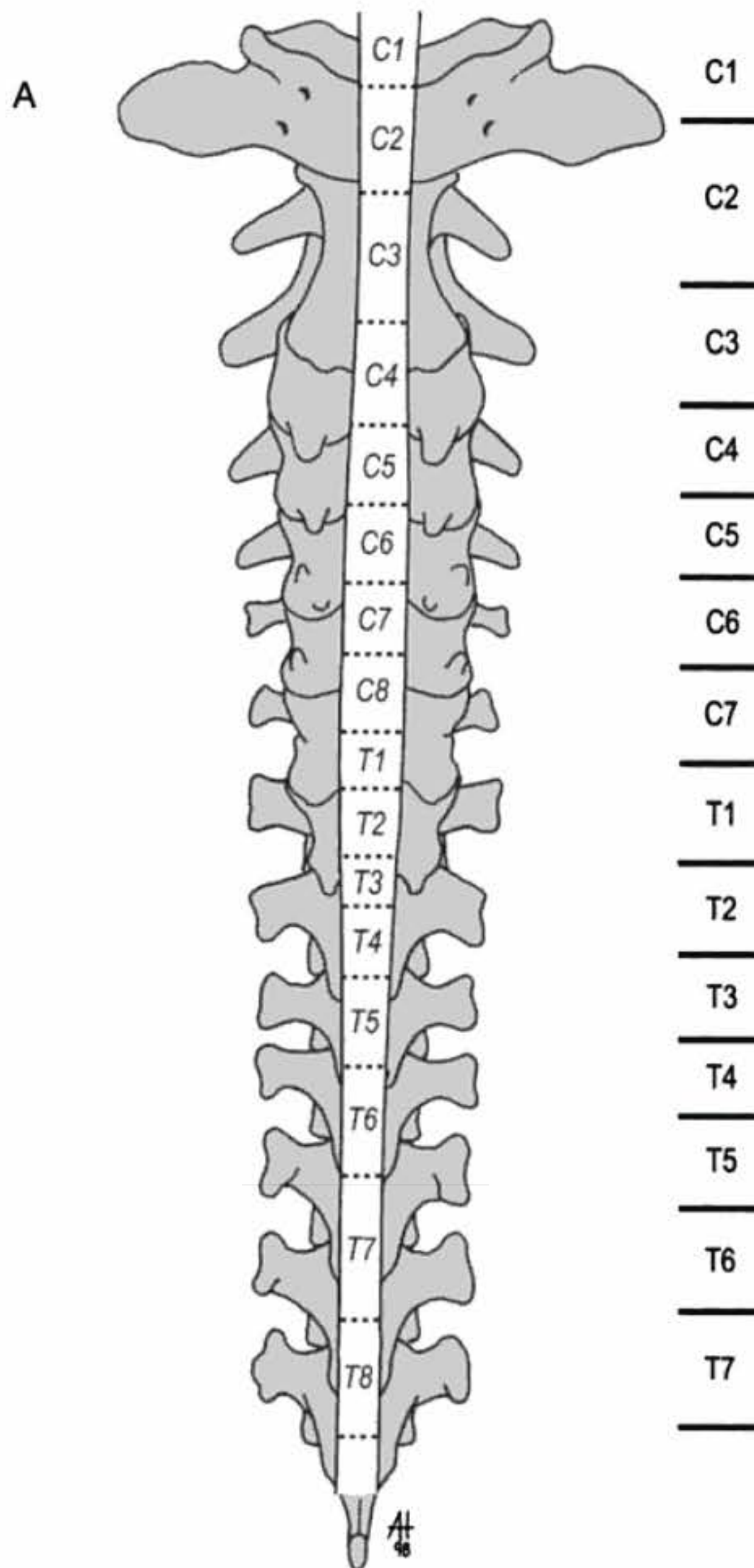


Fig. 1.9. Spinal cord segments and their locations relative to vertebral levels in the dog (Illustration by Anton Hoffman).

perception. The patient must show some behavioral response to the noxious stimulus (e.g., vocalization, attempting to bite) for pain perception to be judged intact.

The spinal cord is divided conceptually into segments, primarily based upon the location of LMNs supplying appendicular (limb) musculature. Although there are LMNs throughout the length of the spinal cord, the LMNs of clinical importance are

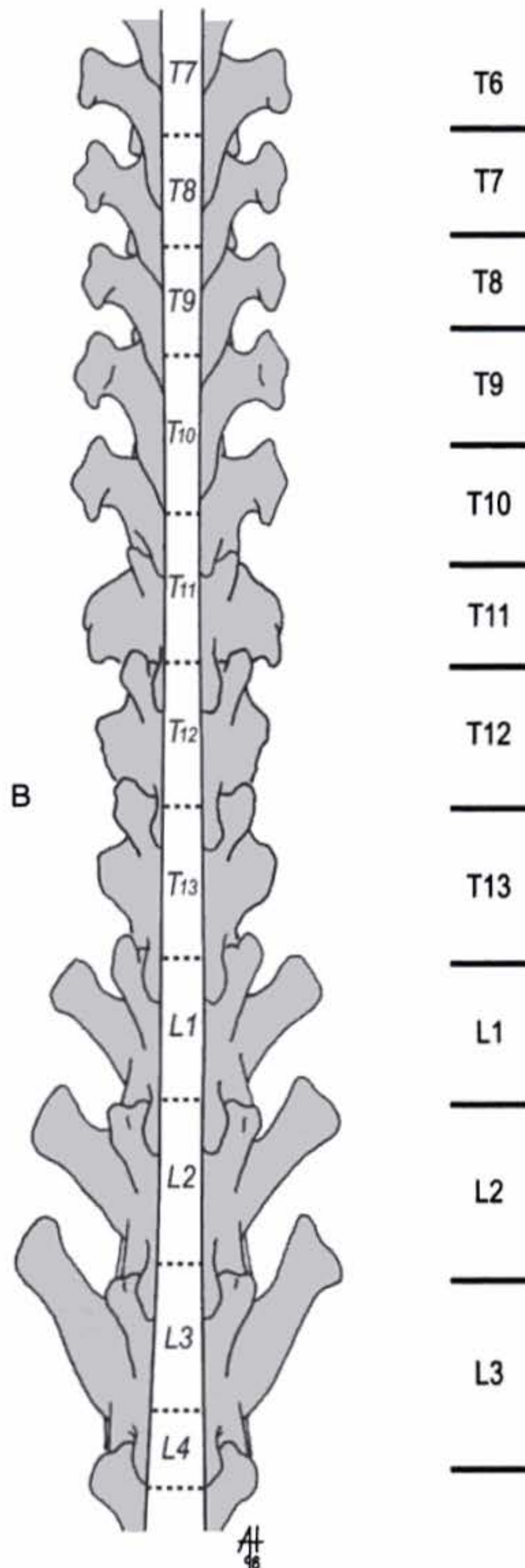


Fig. 1.9. Continued.

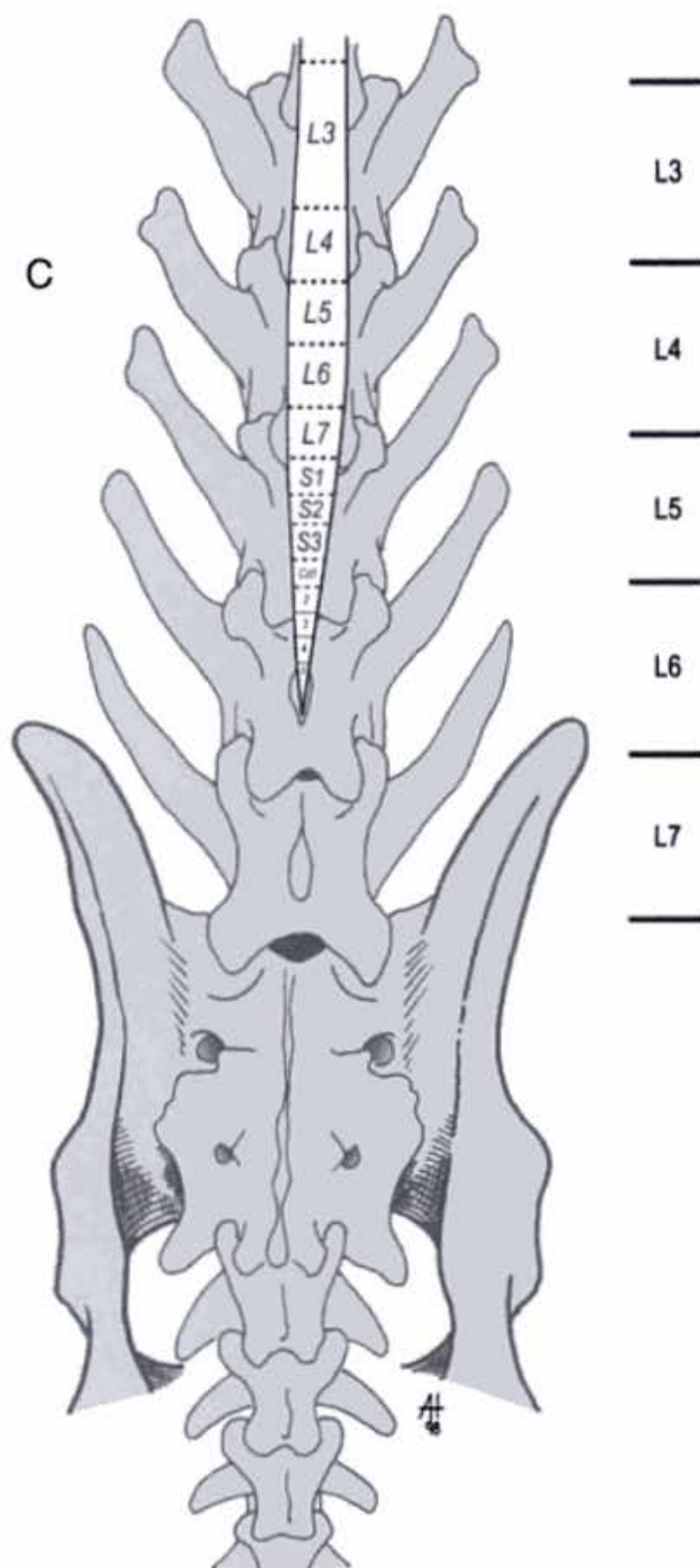


Fig. 1.9. Concluded.

those supplying the limbs, urinary bladder, and anal urethral sphincters. The LMNs of clinical importance are located in the cervical intumescence (C6–T2 segments) and the lumbosacral intumescence (L4–S3 segments) of the spinal cord. Damage to these segments will cause LMN paresis or plegia, characterized by weak to absent reflexes and decreased tone in the associated muscle groups. Damage to areas of the cord without LMNs of clinical significance (C1–C5 and T3–L3) will interrupt descending

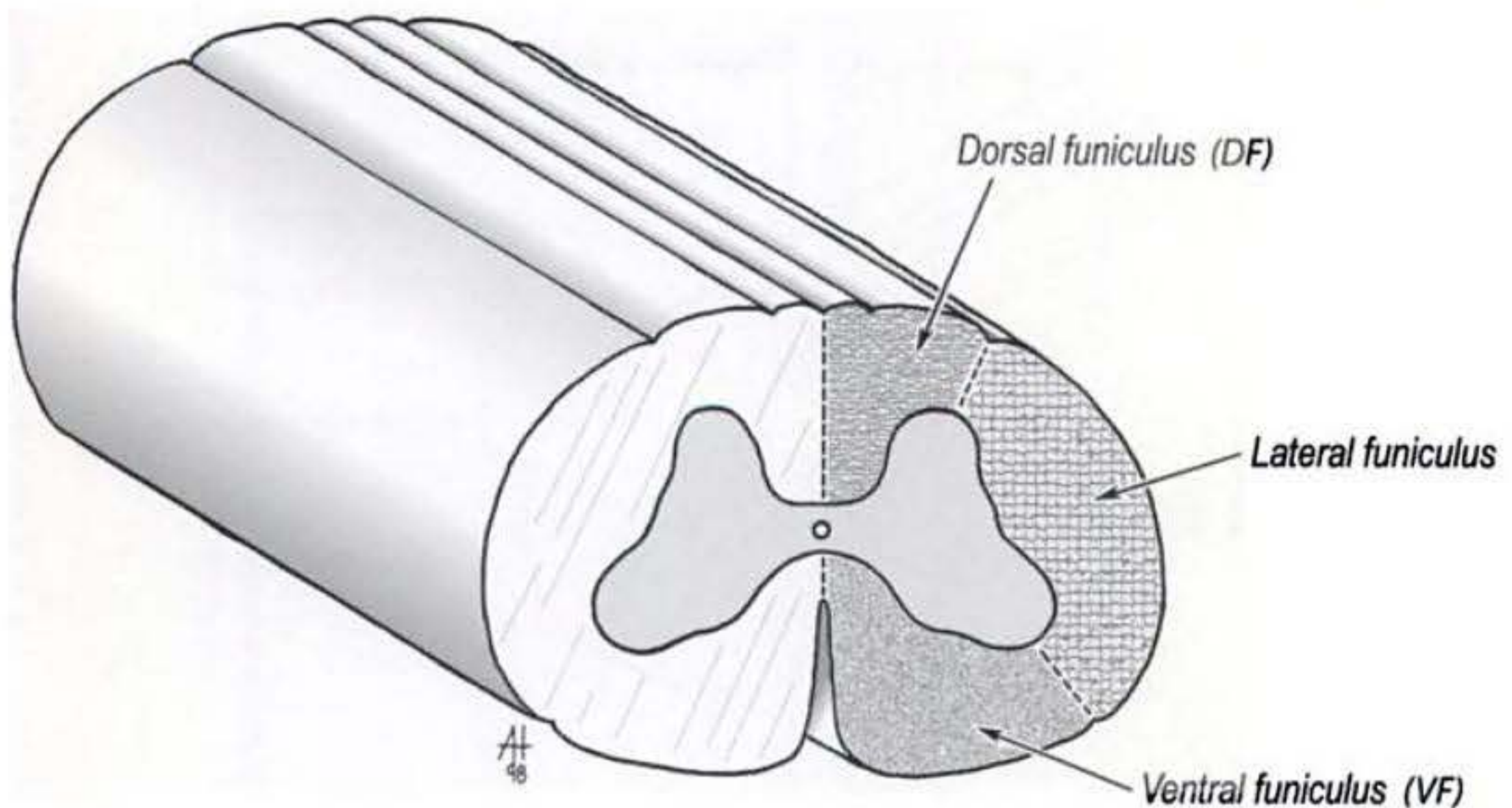


Fig. 1.10. Schematic representation of spinal cord funiculi: DF, dorsal funiculus; LF, lateral funiculus; VF, ventral funiculus (Illustration by Anton Hoffman).

UMN control over the LMNs, leading to UMN paresis or plegia. With UMN paresis/plegia, reflexes and muscle tone will remain either normal or exaggerated.

- A. Cervical and cervicothoracic spinal cord (C1–C5 and C6–T2; see Table 1.3 for clinical signs of spinal cord dysfunction)^{20,29,30}
1. This area of the spinal cord can be divided into cranial (C1–C5) and caudal (C6–T2) cord segments. Lesions in this area of the spinal cord can cause hemiparesis, hemiplegia, tetraparesis, or tetraplegia. Some patients exhibit neck pain only, with no proprioceptive or motor deficits. The clinical signs depend both on the location (i.e., unilateral, dorsal, ventral) and the extent of the lesion.
 2. C1–C5 lesions should cause UMN signs to the thoracic limbs and pelvic limbs; C6–T2 lesions can cause LMN signs in thoracic limbs (if involving the grey matter of C6–T2) and UMN signs in the pelvic limbs.
 3. The lateral tectotegmentospinal tract (sympathetic fibers) travels through the lateral funiculus of the cervical cord and synapses occur with neurons of the intermediolateral grey column nuclei at cord levels T1–T3. Damage to this tract or the cranial thoracic grey matter may result in a Horner's syndrome ipsilateral to the lesion.
 4. The phrenic nerve is formed from neurons in cord segments C5–C7, so damage to these segments may compromise respiratory function.
 5. The lateral thoracic nerve (efferent arm of the cutaneous trunci reflex) is derived from neurons in cord segments C8–T1, so damage to this area of the

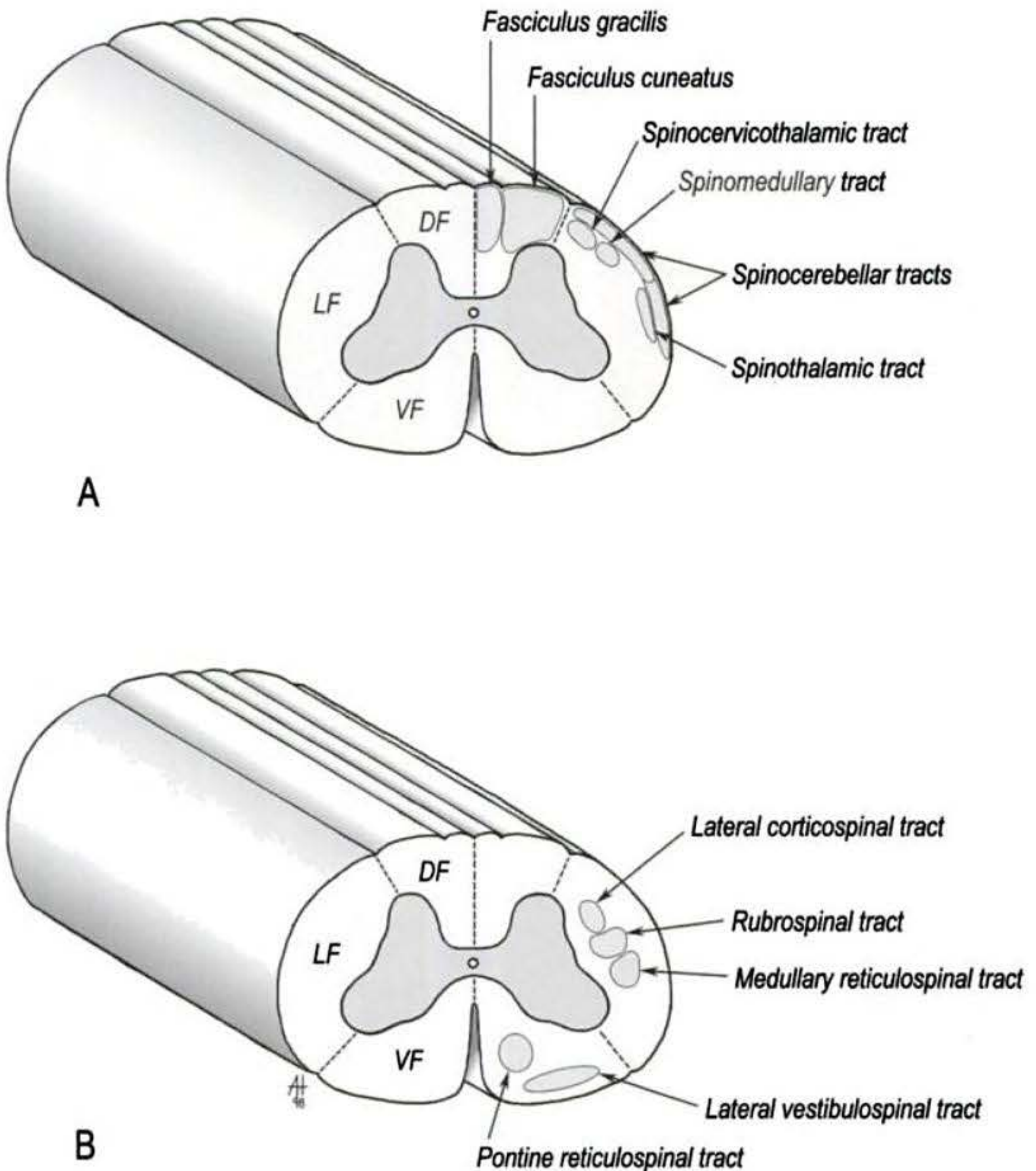


Fig. 1.11. Important ascending (A) and descending (B) spinal cord tracts (Illustration by Anton Hoffman).

spinal cord may result in a decreased or absent cutaneous trunci (panniculus) reflex.

6. Cranial nerves are normal (as opposed to brain-stem disease), with the possible exception of sympathetic dysfunction of the eye(s).
7. Lesions of this area of the spinal cord may result in an "UMN bladder" (see Chapter 11).

Table 1.3: Neurologic Signs of Spinal Cord Dysfunction

Evaluations	Clinical signs			
	C1–C5	C6–T2	T3–L3	L4–caudal segments
Mental status	Normal	Normal	Normal	Normal
Posture	Normal; wide-base stance all limbs, recumbent; horizontal neck carriage	Normal; wide-base stance all limbs, recumbent; +/– horizontal neck carriage	Normal; falling	Normal; falling
Gait	Normal, spastic/dysmetric, ataxia (PL > TL), tetraparesis/plegia, ipsilateral hemiparesis/plegia	Normal, spastic, ataxia (PL > TL), tetraparesis/plegia, ipsilateral hemiparesis/plegia	PL ataxia, symmetric symmetric or asymmetric paraparesis/plegia	PL ataxia, symmetric or asymmetric (more often with cauda equina) paraparesis/plegia
Cranial nerves	Normal; bilateral or ipsilateral Horner's syndrome	Normal; bilateral or ipsilateral Horner's syndrome	Normal	Normal
Postural reactions	Normal, mild-severe deficits (PL > TL); absent	Normal, mild-severe deficits (PL > TL); absent	Mild-severe deficits; absent	Mild-severe deficits; absent
Spinal reflexes	Normal, hyperreflexia all limbs	Normal, hyporeflexia or absent reflexes TL; normal to hyperreflexia PL	Normal, hyperreflexia PL	Hyporeflexia; absent; pseudohyperreflexic patellar reflex with ischiatic dysfunction
Spinal hyperesthesia	None; mild-severe; resists neck movements	None; usually mild; may resist neck movement	None; mild-severe	None; mild-severe
Pain perception	Usually normal; severe lesions may show mild-severe sensory loss	Usually normal; severe lesions may show mild-severe sensory loss	Mild-severe sensory loss; absent	None; mild-severe (more common with intumescence lesion) sensory loss
Micturition	Usually intact; may have detrusor areflexia-sphincter hypertonia	Usually intact; may have detrusor areflexia-sphincter hypertonia	Usually affected with loss of motor function, detrusor areflexia-sphincter hypertonia	None; mild-severe detrusor areflexia-sphincter hypotonia

Source: Courtesy of Dr. Joan Coates.

Note: The sympathetic innervation to the eye (Fig. 1.12) continues from the synapses at T1–T3 (the preganglionic nuclei). The axons of these nuclei join the vagosympathetic trunk in the dorsal thorax, travel up the neck with the vagosympathetic trunk, and leave the trunk near the base of the skull to synapse in the cranial cervical ganglion. Axons from the postganglionic neurons project from here through the tympanooccipital fissure, and the middle ear cavity, and exit the skull as components of the ophthalmic nerve, a branch of the trigeminal (CN V). A Horner's syndrome (ptosis, miosis, enophthalmos) can be caused by damaging the sympathetic system at a number of locations.

B. Thoracolumbar spinal cord (T3–L3)^{27,29,30}

1. This area of the spinal cord can be conceptually divided into T3–L3 segments.
2. The thoracic limbs are neurologically normal. T3–L3 lesions cause signs of UMN dysfunction in the pelvic limbs.
3. Border cells in the dorsolateral border of the ventral grey column of L1–L7 (mainly L2–L4) are neurons that project to the cervical intumescence, providing tonic inhibitory activity to muscles of the thoracic limbs. Disruption of these neurons or their ascending processes can result in disinhibition, usually manifested as thoracic limb extensor rigidity. This posture is known as the “Schiff-Sherrington” phenomenon.
4. Lesions of this area of the spinal cord may result in an “UMN bladder” (see Chapter 11).

C. Lumbosacral and caudal spinal cord (L4–Cd5)^{20,24,26,29,30}

1. This section of the spinal cord comprises the L4–Caudal (Cd) segments. Lesions anywhere along this large area will lead to signs of LMN dysfunction. Because lesions in particular areas of this large region can lead to distinctively different types of neurologic dysfunction, there is some clinical utility in dividing this area into L4–L6, L7–S3, and caudal (Cd1–Cd5) segments.
 - a. L4–L6 lesions cause signs of LMN dysfunction in the pelvic limbs, as the neurons in these segments give rise to the femoral nerve. Decreased to absent patellar reflexes, and intact to diminished withdrawal and gastrocnemius reflexes may be observed. The L6 spinal segment contributes to the sciatic nerve (L6, L7, S1, variable S2), so decreased withdrawal and gastrocnemius reflexes are also possible.
 - b. Lesions primarily of the L7–S3 area of the spinal cord cause signs of LMN dysfunction in distribution sites of sciatic (decreased to absent withdrawal and gastrocnemius reflexes), pudendal (decreased to absent perineal [anal] reflex, poor anal tone), and pelvic (atonic “LMN bladder”) nerves. Patellar reflexes may appear hyperactive if the sciatic nerve or its contributing cell bodies are compromised, but the segments supplying the femoral nerve are not damaged (e.g., degenerative lumbosacral stenosis). The quadriceps muscle group is usually opposed by the caudal thigh muscles; the latter

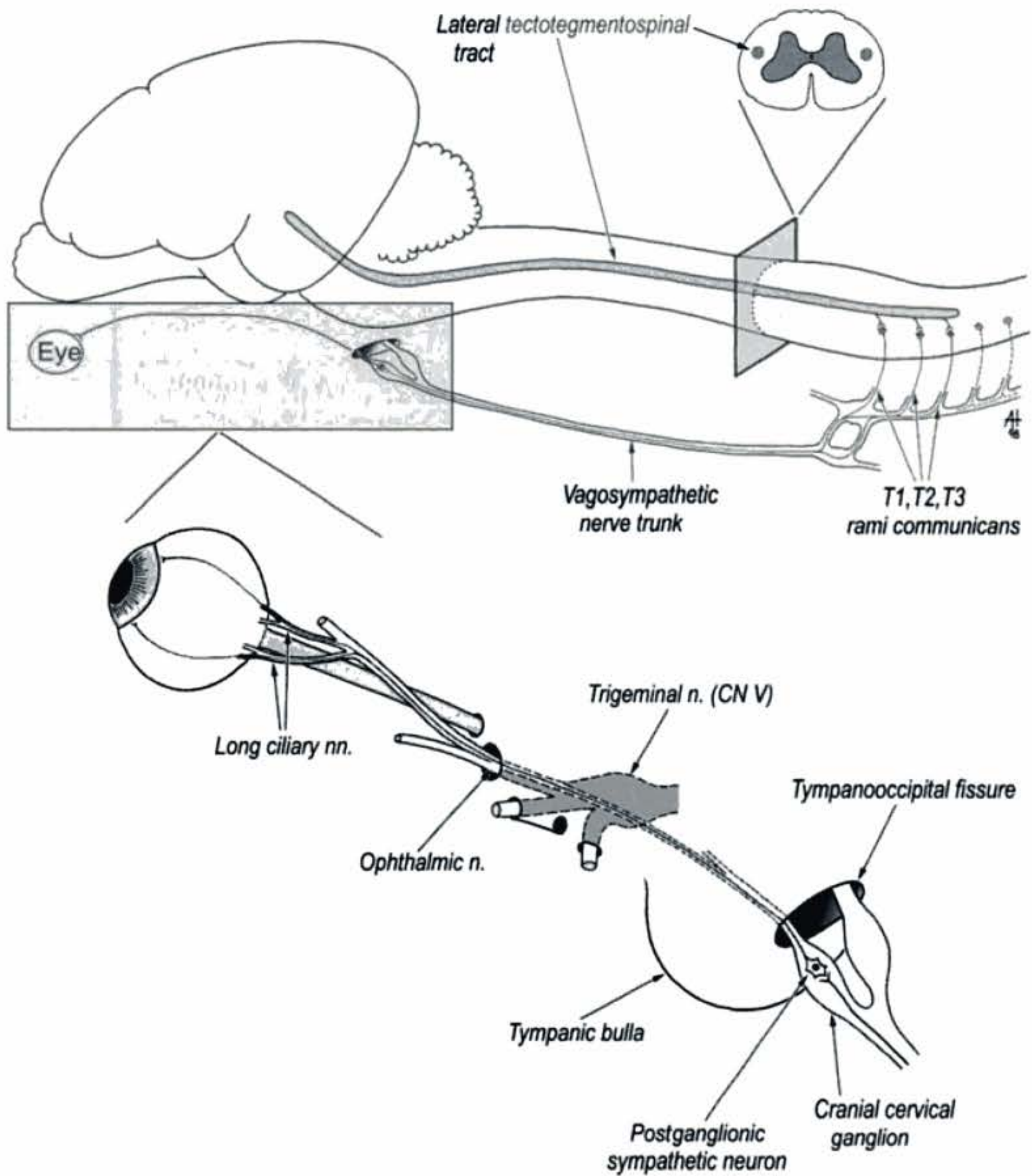


Fig. 1.12. Neuroanatomic pathway for sympathetic innervation of the eye (Illustration by Anton Hoffman).

tend to dampen the patellar reflex (they cause stifle flexion) in the normal dog and cat.

- c. The terminal spinal cord segments are referred to as caudal or coccygeal segments (Cd1–Cd5). These segments contain the LMNs supplying tail musculature, so their dysfunction is manifested by paresis or plegia of the tail.

IV. The Peripheral Nervous System

This neuroanatomic localization includes peripheral nerve, skeletal muscle, and neuromuscular junction (NMJ). Neuronopathies are diseases in which premature degeneration of neuronal cell bodies occurs. Since dogs and cats with neuronopathies display clinical signs similar to or indistinguishable from animals with neuropathies, this disease category is included under peripheral nerve disorders in this text. While disorders of this category are not as common as brain and spinal cord disorders, they are not rare as a group. Many of these disorders have a diffuse distribution (e.g., polyradiculoneuritis), whereas others may appear relatively focal (e.g., idiopathic facial paralysis/paresis). These disorders are usually readily distinguishable from brain and spinal cord problems. It may be difficult to distinguish neuropathy from myopathy from neuromuscular junction disorders. This is not of major importance, as the diagnostic tests used to further characterize all of these disorders are similar. Refer to Table 1.4 for clinical signs of peripheral nervous system dysfunction.

A. Peripheral nerve^{24,31}

1. There are often reduced or absent reflexes, with variable proprioceptive deficits.
2. There is often reduced or absent muscle tone.
3. Depending on the specific disorder, there is a variable distribution of deficits; both mononeuropathies and polyneuropathies are possible (see Chapter 12).
4. Neurogenic muscle atrophy is common. This is rapidly developing muscle atrophy (over 1–2 weeks) due to disruption of nerve supply to the muscle.
5. It may be difficult to discern peripheral nerve disorders from some NMJ disorders.

B. Skeletal muscle^{32,33}

1. Spinal reflexes and proprioception are usually normal.
2. Generalized weakness is frequently evident, often with exercise intolerance.
3. There is usually a bilaterally symmetrical distribution of clinical signs (see Chapter 13 for specific myopathies).
4. Muscle pain on palpation (myalgia) may be appreciated with some myopathies.

C. Neuromuscular junction³⁴

1. Clinical signs of weakness are due to interference of nerve-muscle communication at the level of the neuromuscular junction (see Chapter 14).

Table 1.4: Neurologic Signs of Peripheral Nerve, Neuromuscular Junction, and Muscle Dysfunction

Evaluations	Clinical signs				
	Neuronopathy	Mononeuropathy	Polyneuropathy	Junctionopathy	Myopathy
Mental status	Usually normal; may be obtunded if brain-stem nuclei are affected	Normal	Normal	Normal	Normal
Posture	Progressively unable to support trunk and head	Varies according to affected nerve distribution	May be unable to support trunk or head	May be unable to support trunk, or head may show generalized or focal involvement	Stiff; may hold head/cervical spine horizontal
Muscle mass/ tone	Usually proximal mm. atrophy progressing to distal mm.	Asymmetric limb involvement; rapid and severe atrophy of affected mm.	Generalized and symmetrical rapid and severe atrophy; distal > proximal mm.; +/- mm. flaccidity	Muscle mass usually normal; muscle tone may be flaccid	Usually bilateral, symmetrical generalized atrophy; may have manifest bulk; may have asymmetry; joint contracture
Gait	Tetraparesis; variations in severity of thoracic vs. pelvic limb involvement	Monoparesis/ plegia	May be stilted; tetraparesis /plegia	Episodic paresis; PL may be more severely affected, stilted	Tetraparesis; episodic; exercise intolerance; stilted gait
Cranial nerves	May be affected; may manifest dysphonia, megaesophagus	May be affected	May be affected; facial paresis, dysphonia	May be affected; facial paresis, megaesophagus, dysphonia	May observe severe loss muscle mass of masticatory mm.

continues

Table 1.4: *Continued*

Evaluations	Clinical signs				
	Neuronopathy	Mononeuropathy	Polyneuropathy	Junctionopathy	Myopathy
Postural reactions	Decreased-absent; limb involvement may vary	Decreased-absent in affected limb	Decreased-absent in all limbs	Decreased-absent	Normal, decreased-absent
Spinal reflexes	Usually decreased to absent	Decreased-absent in affected limb	Decreased-absent in all limbs	Normal, decreased, absent	Normal, decreased, absent
Spinal hyperesthesia	None	None	Usually none (except polyradiculoneuritis)	None	Pain may be present upon palpation with some disorders
Pain perception	Normal	Dermatomal hypesthesia or analgesia	Usually normal, +/- paresthesia	Normal	Normal
Micturition	Usually normal until late in disease course	Usually not affected unless S1-S3 spinal nerves are involved	May manifest detrusor/sphincter hypotonia	Usually normal	Usually normal

Source: Courtesy of Dr. Joan Coates.

Note: mm. = muscles.

2. Reflexes may be normal, depressed, or absent, depending on the specific disorder and severity.
3. There is a tendency for diffuse distribution of signs.
4. Exercise intolerance may be noted.
5. Some NMJ disorders may be indistinguishable clinically from a neuropathy or myopathy without further diagnostics.

V. Anatomy of the Spinal Reflexes

In the normal animal, spinal reflexes operate under the influence of descending UMN influence from the brain. However, spinal reflexes remain intact, and are sometimes even exaggerated, if UMN influence is attenuated or abolished. An extreme example of this concept is *spinal walking*. Occasionally, weeks to months after a complete transection injury to the T3–L3 region of the spinal cord in a dog or cat, the patient will develop rhythmic walking movements in the pelvic limbs. The walking movements are due to coordinated reflex patterns that develop within the spinal cord, without any input to or information from UMNs. This “walking” can be induced by stimulating the patient’s pelvic limbs, and sometimes by stimulating nearby areas (e.g., tail, perineum). These animals have no deep pain perception (nociception) to the pelvic limbs, and the pelvic limb movements are not coordinated with the thoracic limbs.³⁵ The following is a simplified description of the anatomy involved in withdrawal and tendon (stretch) reflexes.

A. Withdrawal reflex³⁶

1. The withdrawal reflex is a coordinated polysynaptic reflex, in which all the flexor muscles of a limb contract in response to a noxious stimulus.
2. During the withdrawal reflex, alpha motor neurons to the limb flexor muscles are stimulated, while those to extensor muscles are inhibited. This phenomenon is called *reciprocal innervation*.
3. The force and duration of the withdrawal reflex are proportional to the intensity of the noxious stimulus applied.

B. Tendon (stretch) reflex³⁶

1. The stretch reflex (e.g., patellar reflex) is primarily a monosynaptic reflex. Afferent axons from a muscle stretch receptor directly synapse with spinal cord alpha motor neurons, which cause contraction of that same muscle (Fig. 13.13).
2. The stretch receptor for the tendon reflex is a structure called the *muscle spindle*, located deep within the main muscle belly. The muscle spindle contains specialized muscle fibers called intrafusal fibers, which are arranged in parallel with the main muscle (extrafusal) fibers.
3. The intrafusal muscle fibers of the muscle spindle are made up of polar contractile ends and a central, noncontractile region. Sensory endings of Ia affer-

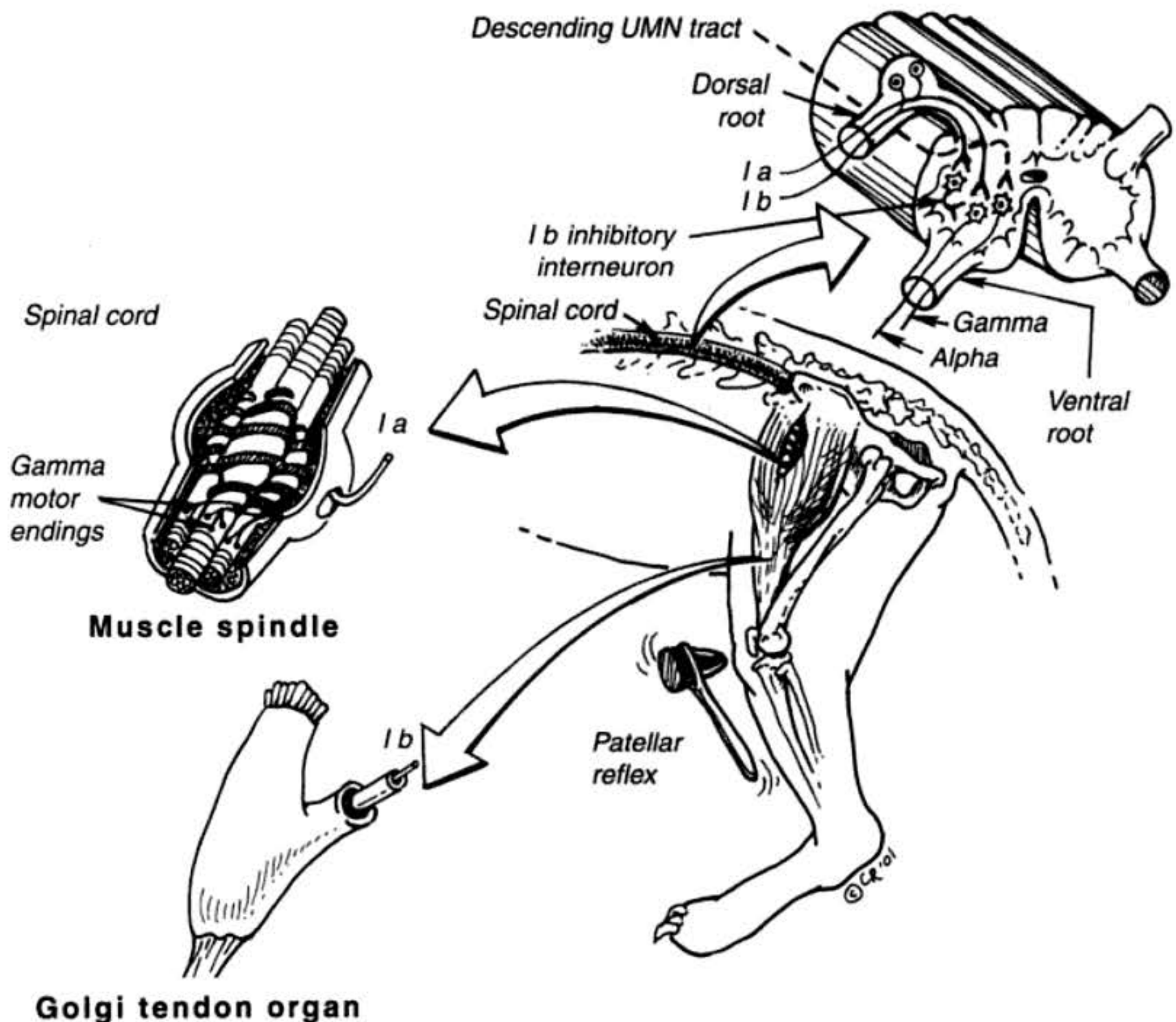


Fig. 1.13. Schematic representation of the tendon (stretch) reflex (Illustration by Carol Rudowsky).

ent axons contact the central regions of the intrafusal fibers. When the central region is stretched (i.e., striking the tendon), action potentials are generated in the Ia axons. The Ia axons enter the spinal cord synapsing with, and exciting alpha motor neurons innervating the extrafusal muscle fibers. Collaterals of Ia axons within the spinal cord also excite Ia inhibitory interneurons. These interneurons synapse with, and decrease activity of, alpha motor neurons that innervate antagonistic muscle groups. When the muscle contracts, the central region of the intrafusal fibers relaxes, decreasing the firing rate of Ia axons.

4. The sensitivity of the muscle spindle can be altered by UMN input to gamma motor neurons. Gamma motor neurons are excitatory neurons that directly innervate the contractile ends of intrafusal muscle fibers. UMN excitation or

inhibition of gamma motor neurons can increase or decrease sensitivity of the muscle spindle to stretch, respectively.

5. The duration and force of muscle contraction associated with a tendon reflex is mitigated to some degree by another receptor called the *golgi tendon organ*. The golgi tendon organ is a group of sensory nerve endings intertwined with collagen fibers at the musculotendinous junction. These sensory nerve endings give rise to a Ib afferent axon. The sensory endings are sensitive to muscle tension, increasing their firing rate when the muscle contracts. The Ib afferent axon stimulates a spinal cord Ib inhibitory interneuron, which inhibits the alpha motor neuron causing the muscle contraction.

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Chapter 2

PERFORMING THE NEUROLOGIC EXAMINATION

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Curtis W. Dewey

I. Introduction

A thorough neurologic exam can be performed in 10 to 15 min. The main components are evaluation of mental status and behavior, gait and postural reactions, cranial nerves, spinal reflexes, palpation, and pain perception. General observation of mental status, posture, attitude, and gait is performed while taking the history. Once the history is clarified, the remainder of the examination is completed. Based on the presenting complaint, it may be necessary to modify portions of the examination. For example, a patient with nonambulatory tetraplegia after being hit by a car is not subjected to postural reactions for fear of exacerbating a possible unstable cervical injury. Start with procedures least likely to upset the patient. Disagreeable or painful procedures, such as palpating painful areas, are left until the end of the examination. If the clinician upsets the patient early on, it may be difficult to complete the examination. Also, once pain is elicited, the patient will often anticipate further painful stimuli, making it difficult to determine if other procedures are truly painful. The purpose of the various procedures are explained to the client as the examination proceeds. This lessens the client's distress when he or she observes unfamiliar procedures performed on a pet. Some abnormalities will be blatantly obvious, whereas others will be subtle. A subtle abnormality is still an abnormality. There is a tendency for subtle abnormalities to be chalked up to anything but a neurologic lesion; trust your neurologic findings.

II. Tools for Performing the Neurologic Examination

A pleximeter (rubber hammer) is used to test myotatic reflexes. Other instruments, such as scissors, are not recommended because these do not provide a consistent stimulus and appear less professional to the client. A hemostat is often useful when testing for nociception or eliciting a cutaneous trunci reflex. A strong light source is necessary to elicit pupillary light reflexes in excited dogs and cats. Finally, a moistened cotton-tipped applicator stick is recommended for performing the corneal reflex. A light touch with your fingertip is acceptable, but if a client is watching you, it may appear to them that you are poking their pet in the eye.

III. Performing the Neurologic Examination¹⁻⁶

A. Mental status and behavior

1. Before handling the patient, let the patient have the run of the examination room, if ambulatory, and observe the patient's reaction to the surroundings.
2. Mental status should be evaluated both in terms of level and content of consciousness.
 - a. Level of consciousness
 - (1) Alert—the patient responds appropriately to environmental stimuli.
 - (2) Depressed/obtunded—the animal is drowsy but arousable.
Depressed/obtunded dogs and cats are typically inattentive and display little spontaneous activity.
 - (3) Stuporous—the patient is in a sleep state, but arousable with strong stimulus.
 - (4) Comatose—the patient is unconscious and cannot be aroused even with painful stimuli.
 - b. Content of consciousness
 - (1) Refers to the quality of consciousness
 - (2) Dementia/delirium—patient has an alert level of consciousness, but exhibits abnormal behavior and responds inappropriately to stimuli.
3. Abnormal behavior is identified by comparing the patient's behavior to expected behavior for animals of a similar breed and age. The client is often able to bring subtle changes in behavior to the veterinarian's attention.

B. Attitude/posture

1. Attitude refers to the position of the eyes and head in relation to the body. Abnormal head position is often manifested as a head tilt or a head turn. In a patient with a head tilt, one ear is held lower than the other. Unilateral vestibular dysfunction will often cause a head tilt. When an animal develops a head turn, the head is held level, but the nose is turned right or left. Animals with forebrain lesions may tend to turn their heads and circle in one direction.
2. Posture is the position of the body with respect to gravity. Abnormal postures, such as a wide-based stance, are common in dogs and cats with neurologic disease. Several classic abnormal postures indicative of neurologic dysfunction have been described.
 - a. Decerebrate rigidity—due to a brain stem lesion and characterized by extension of all limbs and sometimes opisthotonus (dorsiflexion of the head and neck). A decreased level of consciousness (often stupor or coma) usually accompanies this posture.
 - b. Decerebellate rigidity—due to an acute cerebellar lesion and characterized by opisthotonus, thoracic limb extension, and flexion of the hips. Consciousness is not impaired due to lack of brain-stem involvement.
 - c. Schiff-Sherrington posture—frequently encountered in veterinary practice and caused by a lesion in the thoracic or lumbar spinal segments. Extension of the thoracic limbs (best appreciated in lateral recumbency) with paralysis of the pelvic limbs characterizes Schiff-Sherrington posture.

C. Gait

1. Lameness

- a. Limb pain can cause a limp when the patient tries to bear weight on a painful limb and then quickly plants the contralateral limb to relieve the pain. As a result, the stride of the painful limb is often shortened. When a single limb is severely painful, it is often carried. This is in contrast to a paretic limb, which is often dragged. Lameness is usually caused by orthopedic disease, but some neurologic lesions, such as attenuation or inflammation of a nerve root or spinal nerve by intervertebral disk extrusion or nerve sheath tumor can cause lameness. This form of lameness is often referred to as a “root signature.”
- b. Patients with bilateral limb pain, such as hip disease or ruptured cruciate ligaments may not walk at all or have short-strided, stilted gaits. This can mimic weakness due to neurologic disease.
- c. Lower motor neuron weakness can cause a short-strided gait in the affected limb(s).

2. Ataxia—inability to perform normal, coordinated motor activity that is not caused by weakness, musculoskeletal problems, or abnormal movements, such as tremor. There are three types.

a. Sensory ataxia

- (1) Loss of the sense of limb and body position (conscious proprioception)
- (2) Characterized by clumsiness and incoordination, resulting in a wide-based stance and a swaying gait. The stride of the affected limb(s) is often longer than normal and the toes may drag or scuff the ground.
- (3) Caused by a lesion affecting the general proprioceptive pathways in the peripheral nerve, dorsal root, spinal cord, brain stem, and forebrain

b. Cerebellar ataxia

- (1) Inability to regulate the rate and range of movement (unconscious proprioception)
- (2) Characterized by dysmetria, especially hypermetria—an overreaching, high-stepping gait
- (3) Cerebellar ataxia is caused by cerebellar disease or selective dysfunction of spinocerebellar tracts (less likely).

c. Vestibular ataxia

- (1) Unilateral vestibular lesions cause leaning and falling to one side. Other signs of vestibular disease, such as head tilt and abnormal nystagmus may be evident.
- (2) With bilateral vestibular dysfunction, the patient maintains a crouched position, is reluctant to move, and exhibits side-to-side head movements.

3. Paresis/paralysis

Paresis is a partial loss of voluntary movement. This is manifested as a decreased rate or range of motion, increased fatigability, decreased muscle

tone, or limited ability to perform certain motor acts. Paralysis (plegia) is a complete loss of voluntary movement. Paresis or paralysis indicates a lesion of either the upper motor neuron (UMN) system or the lower motor neuron (LMN) system. It is not possible to discriminate between UMN weakness and LMN weakness based solely on the severity of the weakness.

4. Abnormal movements

- a. Tremor—a rhythmical, oscillatory movement localized to one region of the body or generalized to involve the entire body. A terminal tremor, or intention tremor, occurs as the body part nears a target during goal-oriented movement. This is most evident as a head tremor when the patient attempts to sniff an object, eat, or drink. A postural tremor occurs as the limb or head is maintained against gravity.
- b. Myotonia—delayed relaxation of muscle following voluntary contraction. Myotonia is manifested as muscle stiffness that is relieved by exercise. Attacks of myotonia may culminate in recumbency with rigid extension of the limbs. Some patients with myotonia will display “dimpling” of sustained indentation of affected muscle when percussed.
- c. Myoclonus—a brief, shocklike muscle contraction producing a quick, jerking movement of a body part.

D. Postural reactions

Postural reactions test the same neurologic pathways involved in gait, namely the proprioceptive and motor systems. Their main value is detecting subtle deficits or inconspicuous asymmetry that may not be obvious during the observation of gait. Postural reactions are also useful in discriminating between orthopedic and neurologic disorders.

1. Proprioceptive positioning

- a. Support the animal to avoid body tilt and turn one paw over so that the dorsal surface is in contact with the ground. The patient should immediately return the foot to a normal position (Fig. 2.1).
- b. When properly supported, most patients with orthopedic disease will have normal proprioceptive positioning. On the other hand, proprioceptive pathways are often compromised early in the course of neurologic diseases, so defects in proprioceptive positioning may be detected before there are obvious signs of weakness.

2. Placing response

- a. The nonvisual (tactile) test is performed first. Cover the patient's eyes, pick the animal up and move it toward the edge of a table. When the paw touches the table, the animal should immediately place the limb forward to rest the paw on the table surface (Fig. 2.2).
- b. Visual placing is tested similarly except the patient's eyes are not covered. The normal response is to place the paws on the surface as the table is approached, before the paws contact the table. This test may detect visual deficiencies.

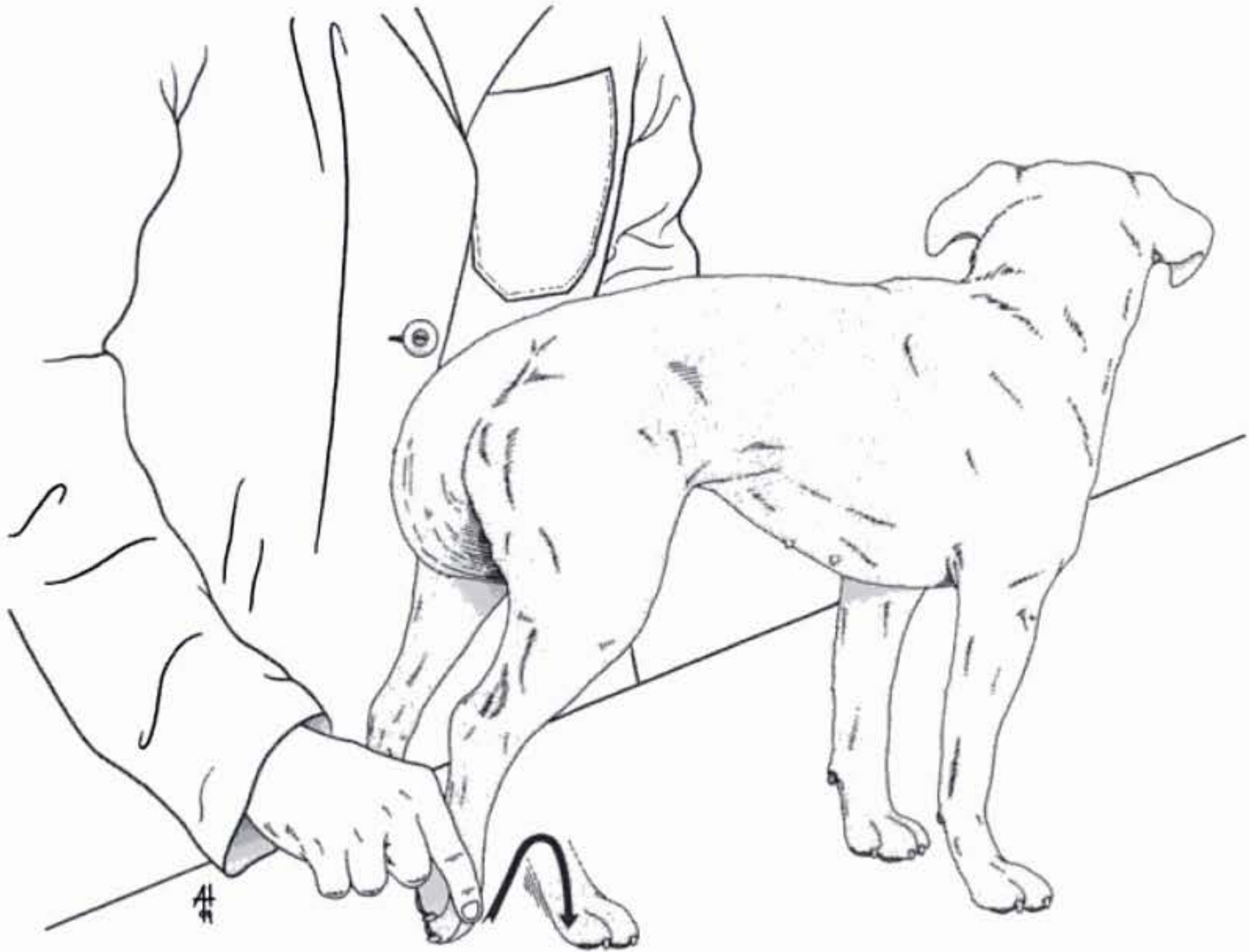


Fig. 2.1. Proprioceptive positioning is evaluated with the animal supported in a standing position. The dorsal surface of the paw is placed on the floor. The patient should immediately replace the foot to a normal position (Illustration by Anton Hoffman).

3. Hopping

- a. Hold the patient so that all the patient's weight is supported by one limb and move the animal forward or laterally (Fig. 2.3). Normal animals will hop on the limb while keeping the foot under their body for support.
- b. Each limb is tested individually and responses on the left and right are compared. This is a sensitive test for subtle weakness or asymmetry.

4. Hemiwalking and wheelbarrowing

- a. These tests can be performed if other postural reactions are equivocal or in large dogs when eliciting the hopping response is physically difficult for the examiner.
- b. For hemiwalking, hold up the limbs on one side of the body and move the patient laterally (Fig. 2.4). The normal reaction is as described for the hopping response.
- c. Wheelbarrowing in the thoracic limbs is done by supporting the patient under the abdomen so that the pelvic limbs do not touch the ground and

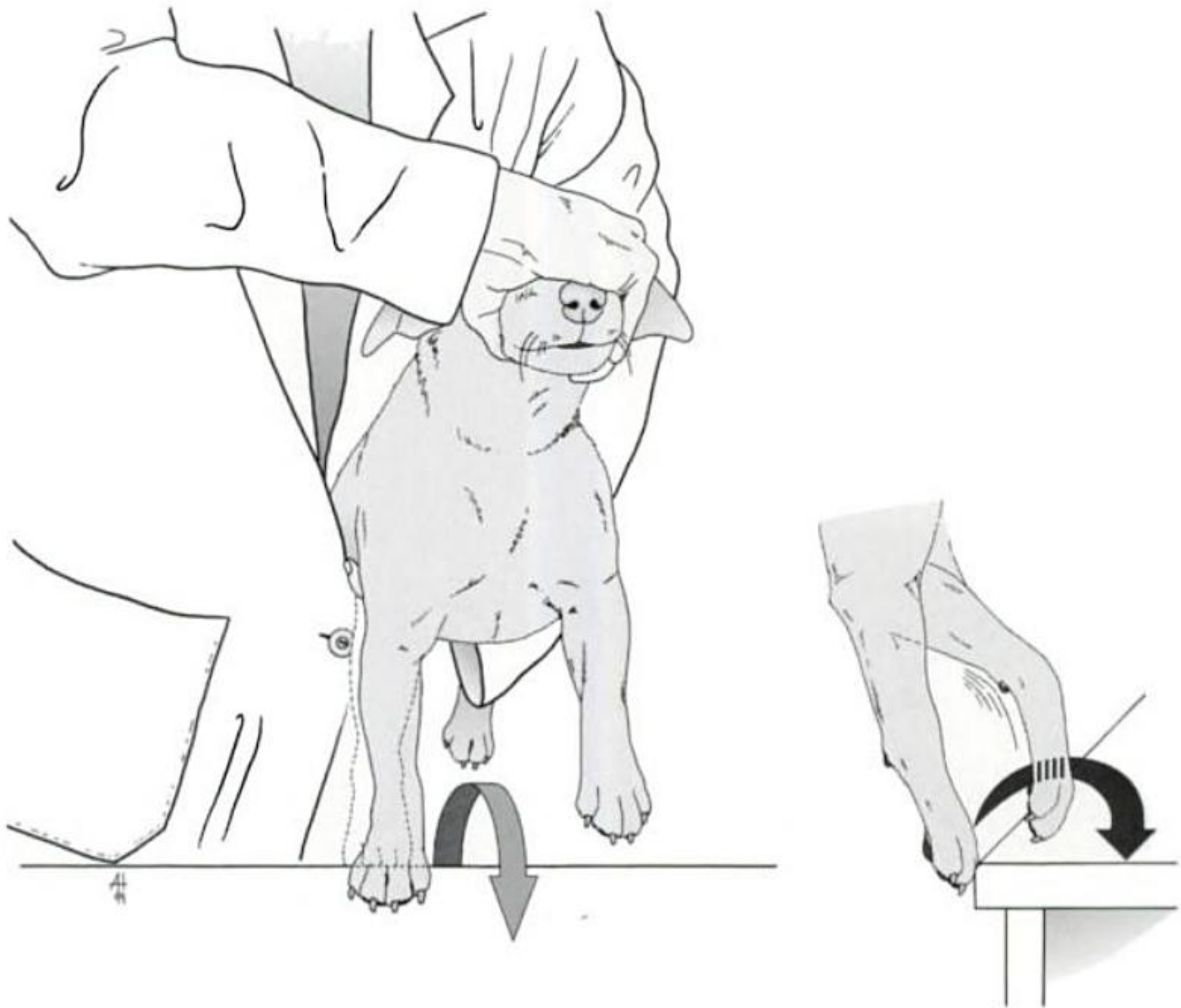


Fig. 2.2. Tactile placing is tested by covering the patient's eyes and moving the patient toward the edge of a table. Normal animals will place their feet on the table as soon as they contact the edge of the table (Illustration by Anton Hoffman).

moving the patient forward (Fig. 2.5). Normal animals will walk with symmetrical, alternate movements of the thoracic limbs.

E. Cranial nerves (Fig. 2.6)

1. CN I (olfactory nerve) is not routinely tested. After ascertaining patency of the nostrils, cover the patient's eyes and present a morsel of food beneath the nose, observing for normal sniffing behavior. Irritating substances, such as ammonia or isopropyl alcohol, should not be used because they stimulate trigeminal nerve endings in the nasal passages and produce false results.
2. CN II (optic nerve)
 - a. Note pupillary size and any anisocoria. There should be a direct and consensual pupillary light reflex in each eye (Fig. 2.7).

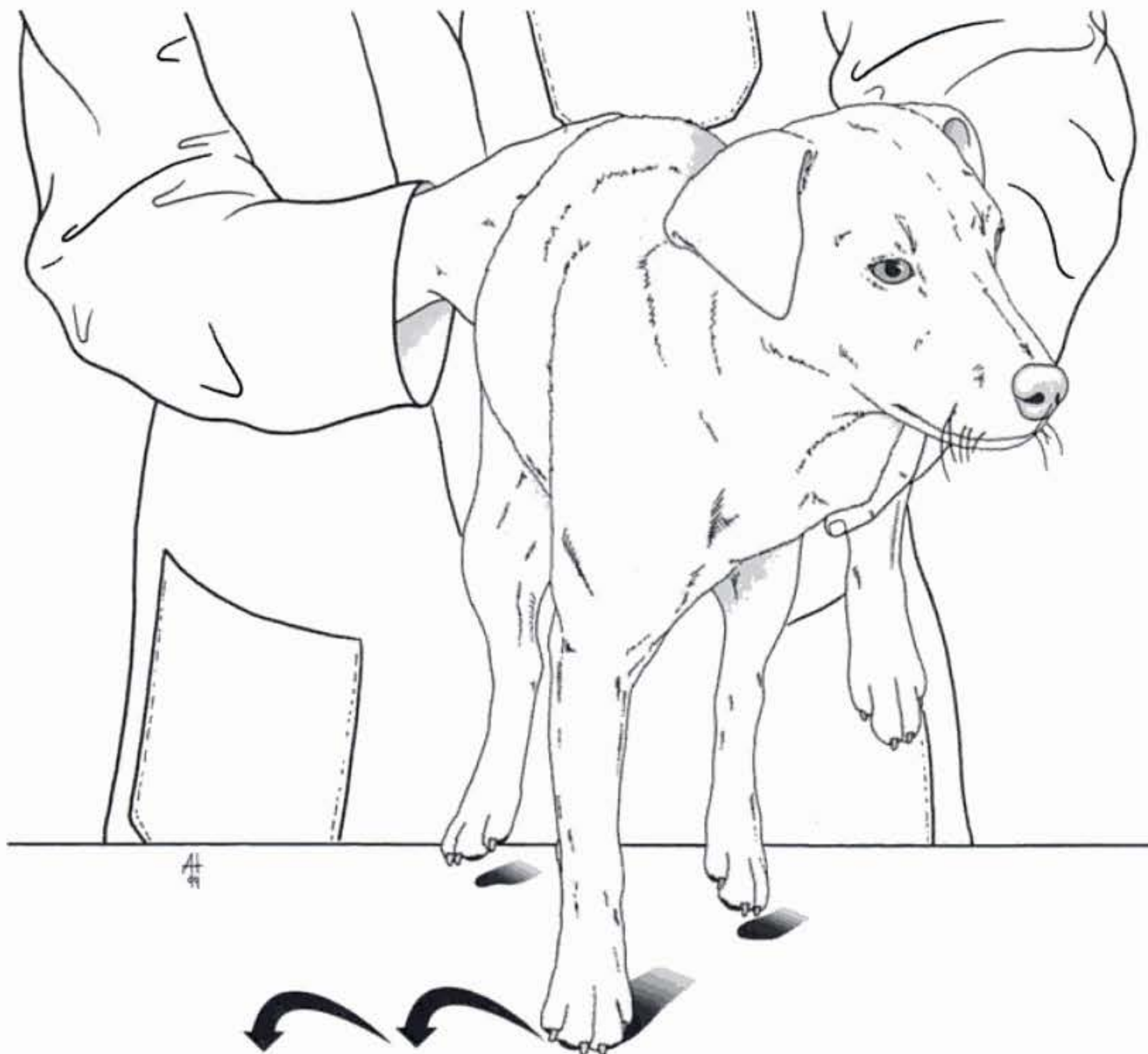


Fig. 2.3. The hopping response is tested by holding the animal such that most of the animal's weight is borne on one limb. The patient is moved laterally (Illustration by Anton Hoffman).

- b. Menace response. Move your hand toward the patient's eyes in a threatening manner, observing for a blink response (Fig. 2.8). By covering the contralateral eye, you can test the nasal (medial) and temporal (lateral) visual fields of each eye. The efferent part of this reaction is controlled by the facial nucleus and nerve (CN VII). The menace response may be deficient in puppies and kittens (less than 12 wk).
- c. Visual following. Drop cotton balls or move a toy or ball in front of the patient and observe if the patient's eyes and head follow the object.



Fig. 2.4. Hemiwalking is tested by lifting the limbs on one side and moving the patient laterally (Illustration by Anton Hoffman).

3. CN III (oculomotor nerve), IV (trochlear nerve), and VI (abducent nerve) are considered together because they control eye movements. CN III also mediates pupillary constriction, which is evaluated by the pupillary light reflex.
 - a. Strabismus may be obvious or can be detected by shining a light on the cornea. When the eyes are aligned, the light reflection is on the same area in each eye.

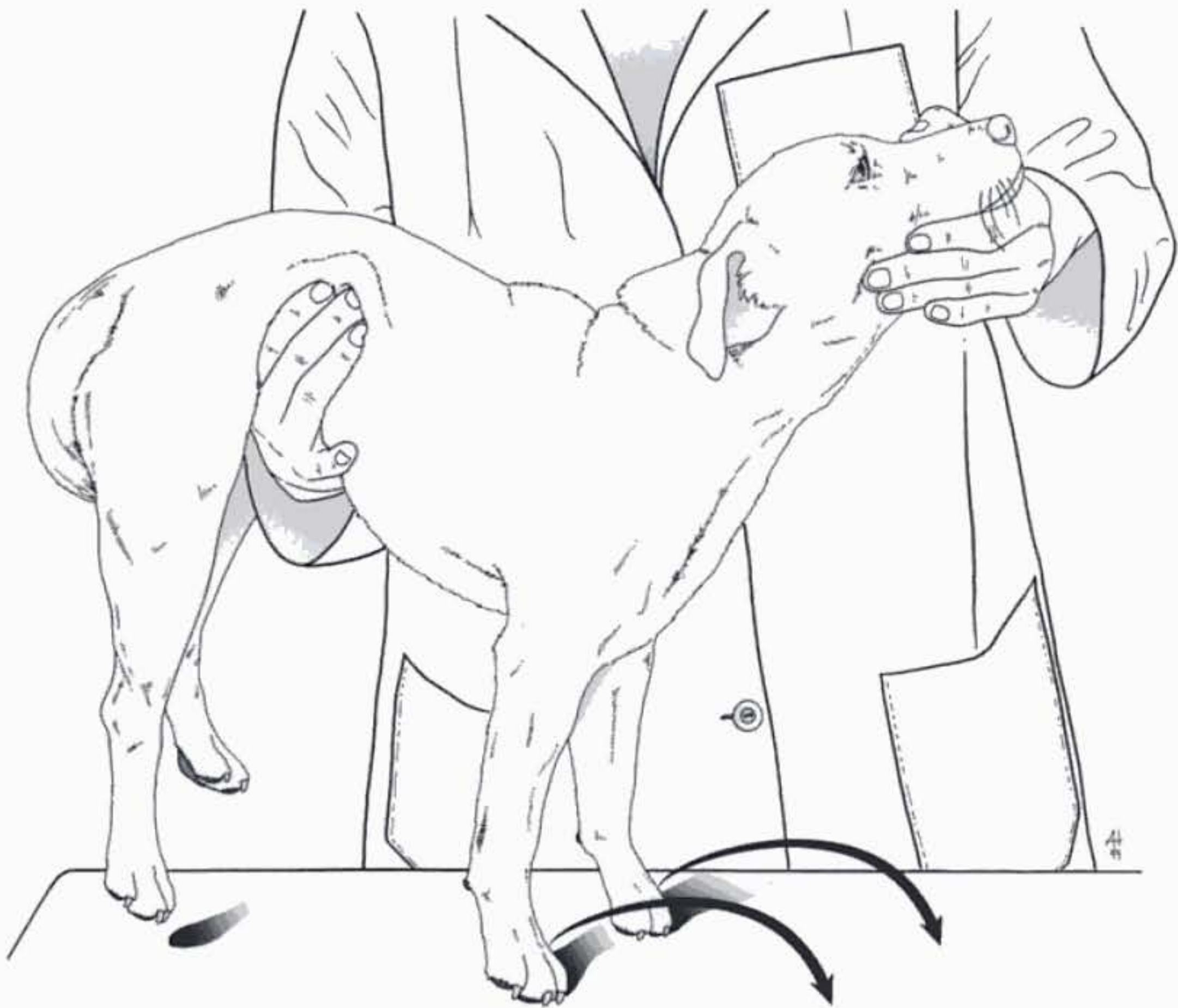


Fig. 2.5. Wheelbarrowing is tested by supporting the patient under the abdomen so that the pelvic limbs do not touch the ground and moving the patient forward (Illustration by Anton Hoffman).

- b. Observe spontaneous eye movements when the patient looks about. Move the patient's head from side to side and up and down to induce horizontal and vertical nystagmus.
- c. To induce the corneal reflex, touch the cornea with a cotton-tipped applicator moistened with saline (Fig. 2.9). Corneal sensation depends on the ophthalmic branch of the trigeminal nerve. The normal response is a retraction of the globe, mediated by the abducent nerve (CN VI).
- 4. CN V (trigeminal nerve)
 - a. Motor portion—The temporalis and masseter muscles are visualized and palpated to detect any swelling, atrophy, or asymmetry. If there is bilateral weakness, the patient may not be able to close the mouth.

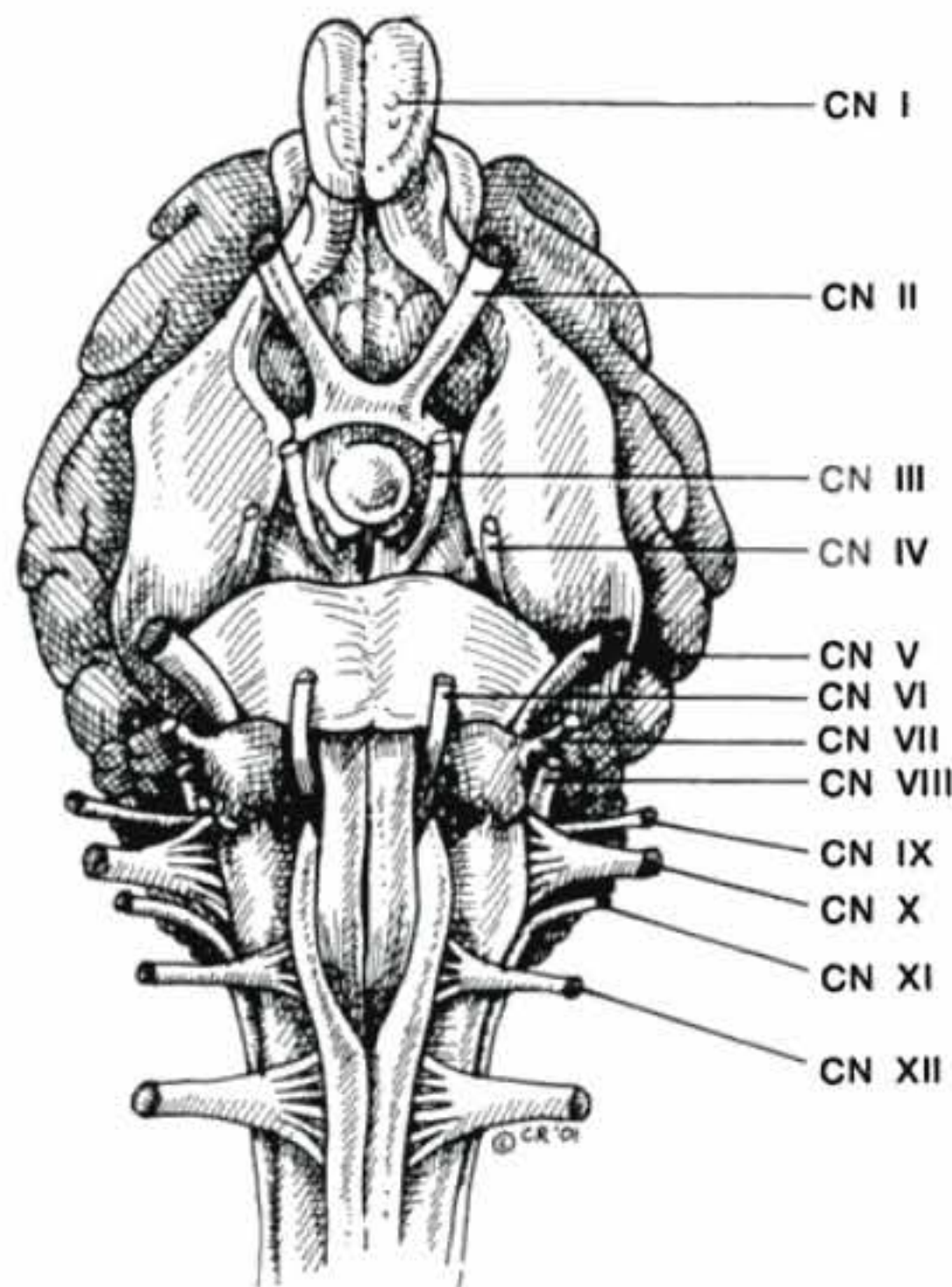


Fig. 2.6. Ventral aspect of the feline brain, showing the relative anatomic positions of the cranial nerves (Illustration by Carol Rudowsky).

b. Sensory portion

- (1) Ophthalmic branch—This branch of CN V can be evaluated via the corneal reflex (discussed above) and by specifically touching the medial canthus of the eyelid region during the palpebral reflex. The efferent part of this reflex is dependent on normal function of the facial nucleus and nerve (CN VII).
- (2) Maxillary branch—Pinch the upper lip lateral to the canine tooth. A normal response is a wrinkling of the face and a blink, which also depends on motor supply by the facial nerve. Some animals also turn or withdraw their head, indicating a conscious response mediated at the level of the forebrain.

In patients who do not respond to pinching the face, gently insert the tip of a hemostat into each nostril (Fig. 2.10). The normal response is to withdraw the head. The mucosa of the inner nare is innervated by both maxillary and ophthalmic branches of CN V.

- (3) Mandibular branch—Pinch the lower lip lateral to the canine tooth. The patient should show a behavioral response.

5. CN VII (facial nerve)



Fig. 2.7. The pupillary light reflex is elicited by shining a bright light in each eye. Normally, there is brisk constriction of the ipsilateral (direct pupillary light reflex) and contralateral pupil (indirect, or consensual pupillary light reflex) (Illustration by Anton Hoffman).

- a. Observe the patient's face for asymmetrical eyelid closure, a widened palpebral fissure, spontaneous blinking, or a drooping ear.
 - b. The ability to blink is tested by eliciting the palpebral reflex (Fig. 2.11).
 - c. The facial nerve also mediates tearing, which is evaluated with Schirmer test strips.
6. CN VIII (vestibulocochlear)
- a. Cochlear portion
 - (1) Alert patients should orient their head and ears toward a loud or unexpected noise, such as a squeaky toy, whistle, or pager/beeper.
 - (2) The client may notice signs of subtle hearing loss. For example, the animal may sleep soundly or not respond readily to being called.
 - b. Vestibular portion



Fig. 2.8. The menace response is elicited by making a threatening gesture at the eye, which should induce a blink (Illustration by Anton Hoffman).

- (1) Signs of vestibular dysfunction include head tilt, abnormal nystagmus, and an ataxic, broad-based stance.
 - (2) Physiologic nystagmus is elicited by rotating the patient's head. Normal physiologic nystagmus has a fast phase in the direction of the head rotation.
 - (3) Putting the head in different positions is done to elicit positional nystagmus or positional strabismus (both are abnormal).
7. CN IX (glossopharyngeal nerve) and CN X (vagus nerve)
- a. Ask the client about any dysphagia, regurgitation, voice change or inspiratory stridor.
 - b. Touch the left or right side of the caudal pharyngeal wall with an applicator stick or finger and watch for elevation of the palate and contraction of the pharyngeal muscles, called the gag reflex (Fig. 2.12). An asymmetrical response is more significant than a bilateral loss of the gag reflex, because this reflex is difficult to elicit in some normal animals. If the patient's

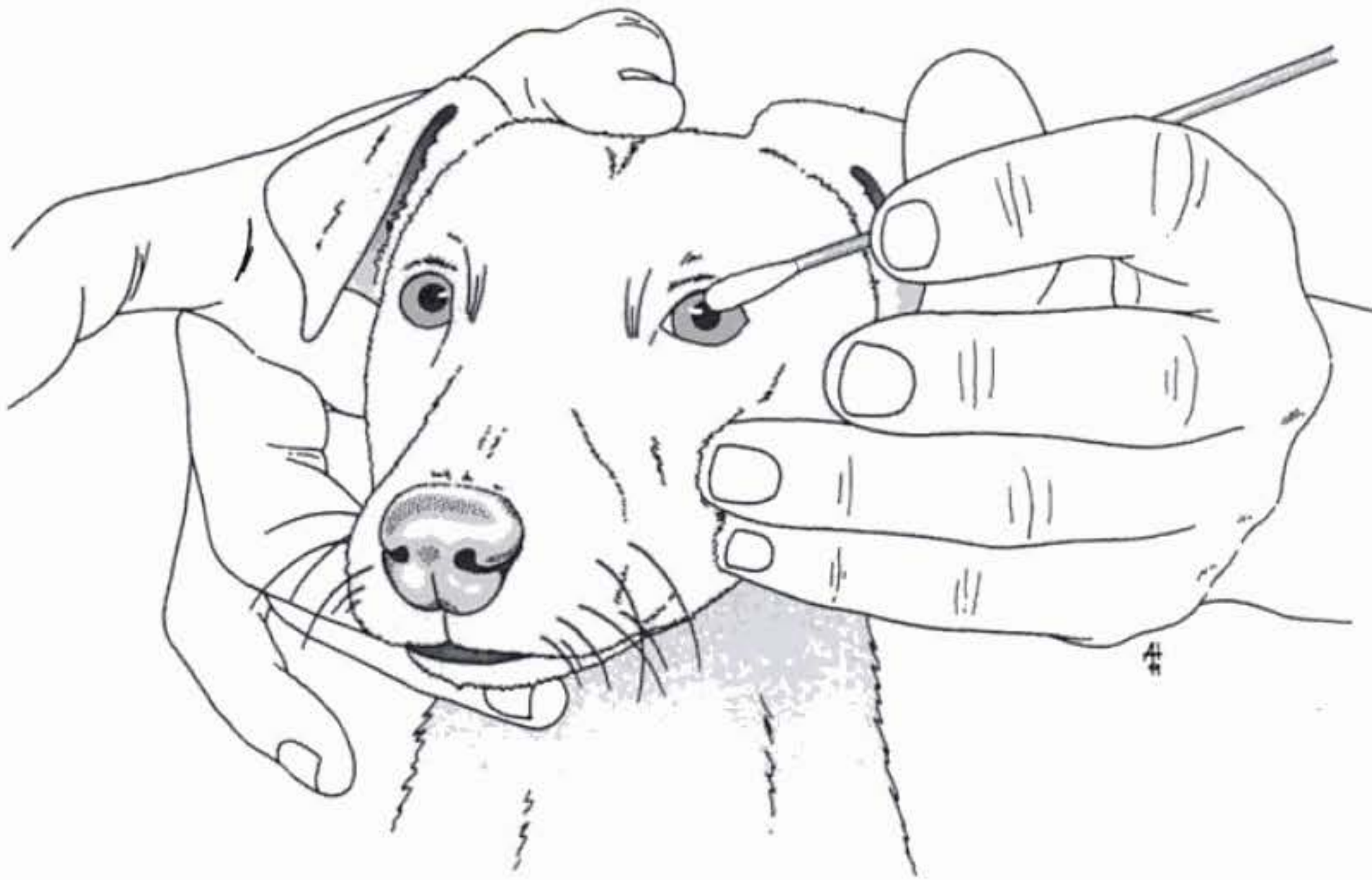


Fig. 2.9. The corneal reflex is tested by touching the cornea with a cotton-tipped applicator moistened with saline. The normal response is a retraction of the globe (Illustration by Anton Hoffman).

demeanor precludes stimulating the pharyngeal mucosa, a similar reflex can sometimes be elicited by externally palpating the pharyngeal region dorsal to the larynx.

8. CN XI (spinal accessory branch) supplies motor innervation to the trapezius muscle. A lesion in this nerve results in atrophy of the trapezius muscle. However, this is difficult to detect in most patients and lesions restricted to this nerve are rarely recognized. The internal branch of CN XI is structurally and functionally part of CN X.
9. CN XII (hypoglossal nerve)
 - a. Inspect the tongue for atrophy, asymmetry, or deviation.
 - b. Animals usually lick their nose immediately after the gag reflex is tested. Patients with unilateral loss of innervation may be able to lick only one side of the nose, with the tongue usually deviating toward the side of the lesion when actively protruded.
 - c. Watching the patient drink water also helps assess tongue function.

F. Spinal reflexes

1. Spinal reflexes assess the integrity of the sensory and motor components of the reflex arc and the influence of descending UMN motor pathways.

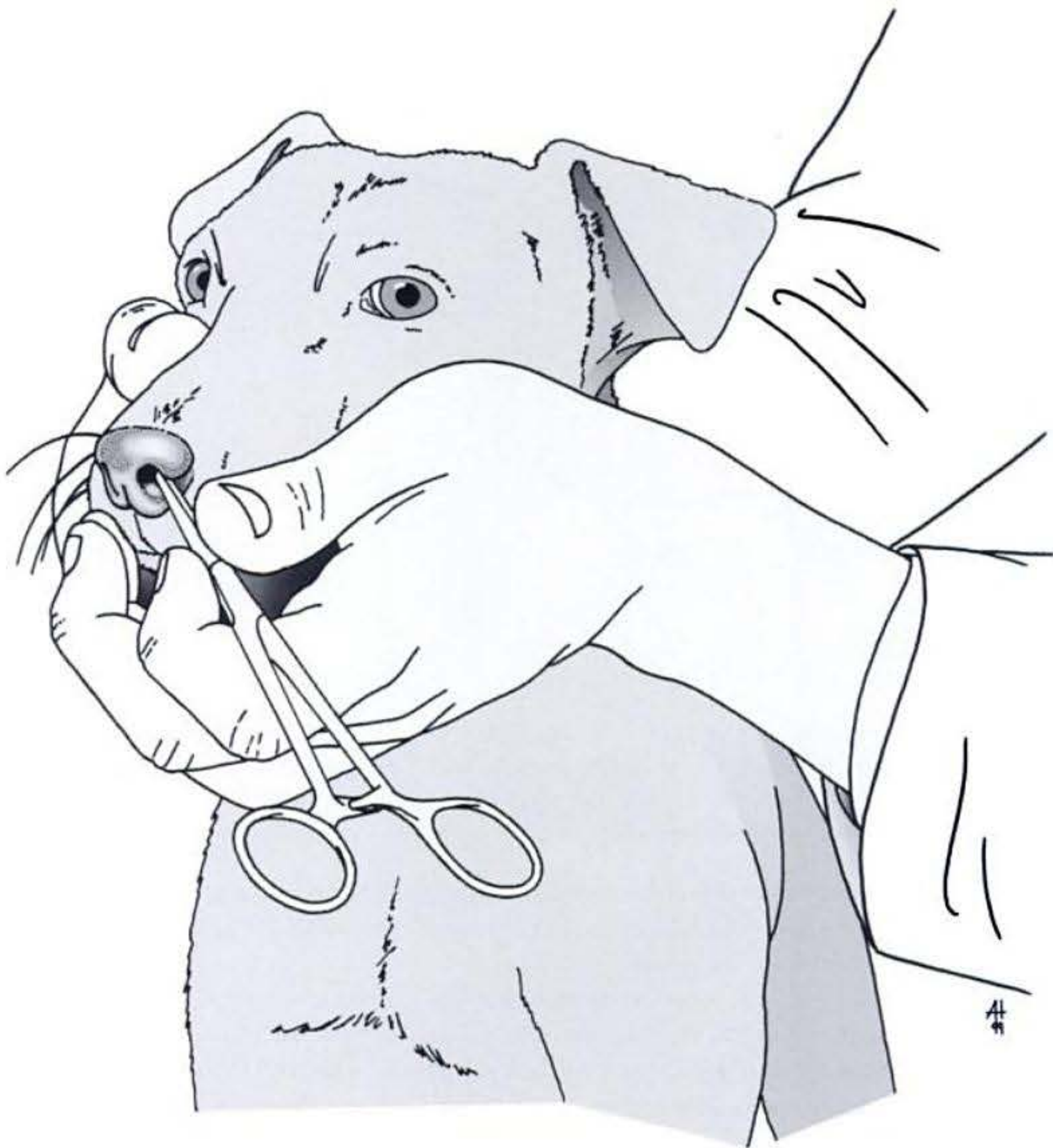


Fig. 2.10. The sensory portion of the trigeminal nerve (CN V) is tested by stimulating the nasal mucosa with a blunt instrument. Normal patients will pull their head away (Illustration by Anton Hoffman).

2. Reflexes are graded as follows:
 - a. Absent
 - b. Weak (present but reduced)
 - c. Normal
 - d. Exaggerated

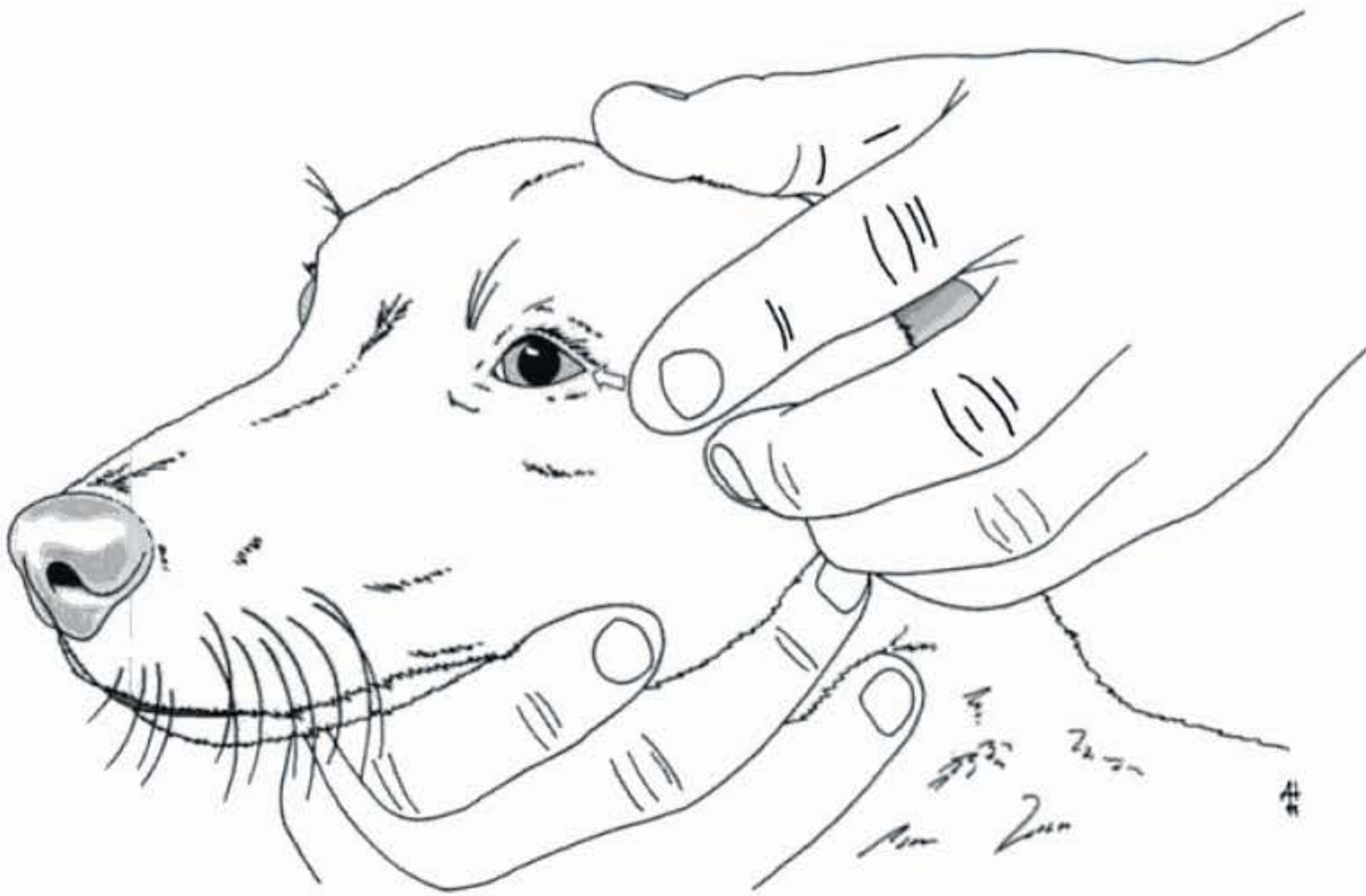


Fig. 2.11. The palpebral reflex is elicited by touching the skin either medial or lateral to the eye. Normally, this will induce a blink (Illustration by Anton Hoffman).

- e. Clonus (repetitive flexion and extension of the joint in response to a single stimulus)
3. Causes of weak or absent reflexes are:
 - a. A lesion affecting any part of the reflex arc, including the peripheral nerve, nerve roots, spinal segments, neuromuscular junction, and muscle. Other signs of weakness are usually apparent.
 - b. Severe rigidity or muscle contraction that limits joint movement, such as fibrosis of a joint or muscle. Absent muscle stretch reflexes can also be seen in normal animals that are excited or unable to relax. In these patients, other signs of LMN weakness are absent.
 - c. Spinal shock, which can occur immediately after severe spinal cord injury. This is characterized by paralysis and absent reflexes caudal to the level of injury. In dogs and cats, spinal shock is short-lived, with reflexes returning within about 30 minutes.
4. Causes of exaggerated reflexes or clonus are:
 - a. A lesion in the UMN pathways cranial to the spinal segment involved in the reflex. Other signs of UMN disease, such as paresis or paralysis, are also evident.

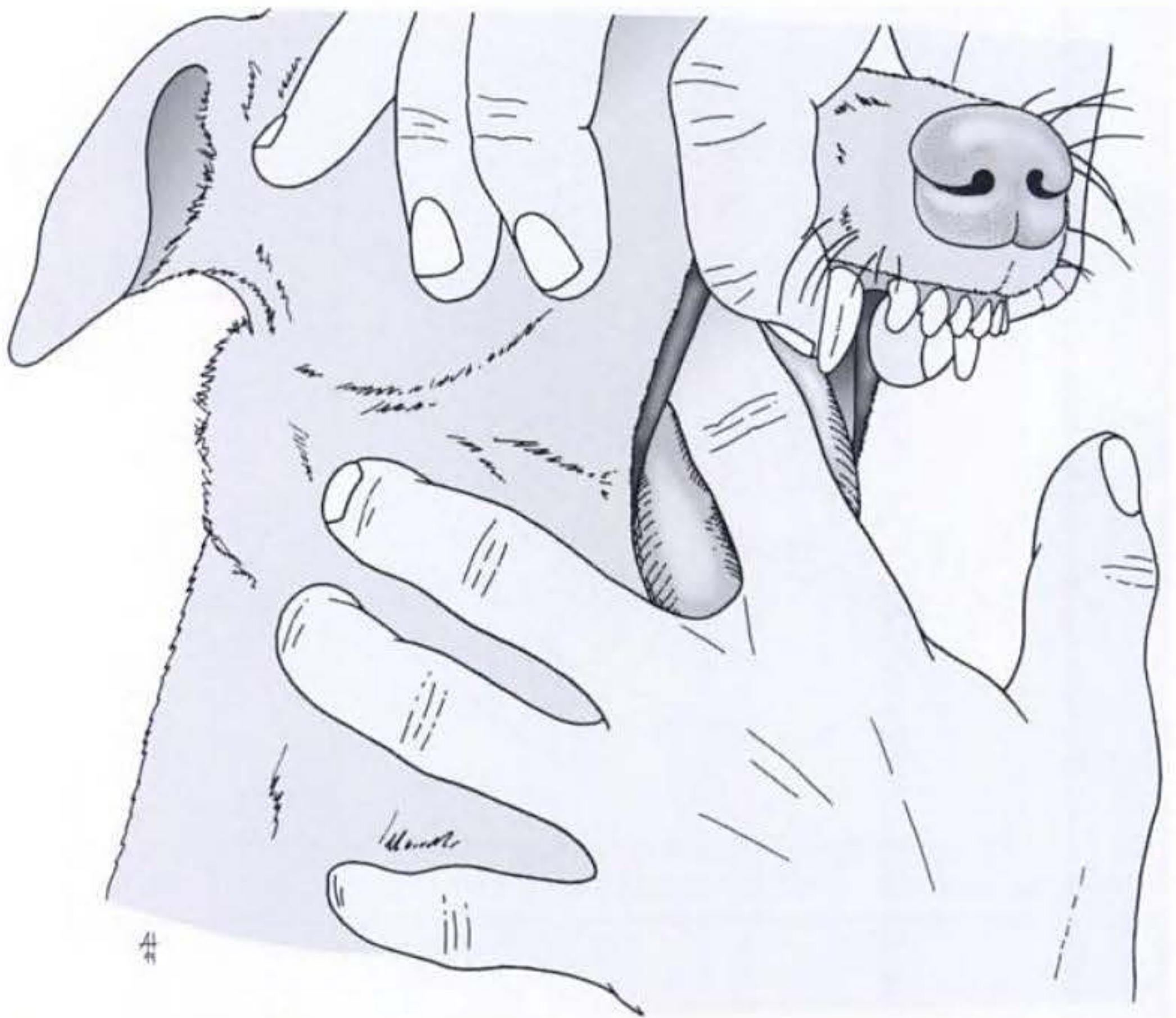


Fig. 2.12. The gag reflex is tested by touching the pharynx and elevation of the palate and contraction of the pharyngeal muscles (Illustration by Anton Hoffman).

- b. Patients that are excited or anxious. In this case, other signs of a UMN lesion are absent. Never diagnose a UMN lesion in a patient with exaggerated reflexes but normal gait and postural reactions.
 - c. A lesion of the L6–S1 spinal segments or sciatic nerve can cause an exaggerated patellar reflex (pseudo-hyper-reflexia). This is due to decreased tone in the muscles that flex the stifle and normally dampen stifle extension when the patellar reflex is elicited. Such lesions also cause other abnormalities, such as a decreased flexor reflex.
5. Patellar reflex
- a. With the patient in lateral recumbency, place one hand under the thigh to support the limb with the stifle in a partially flexed position. With the other hand, briskly strike the patellar ligament (located between the patella and tibial tuberosity) with a reflex hammer (Fig. 2.13).

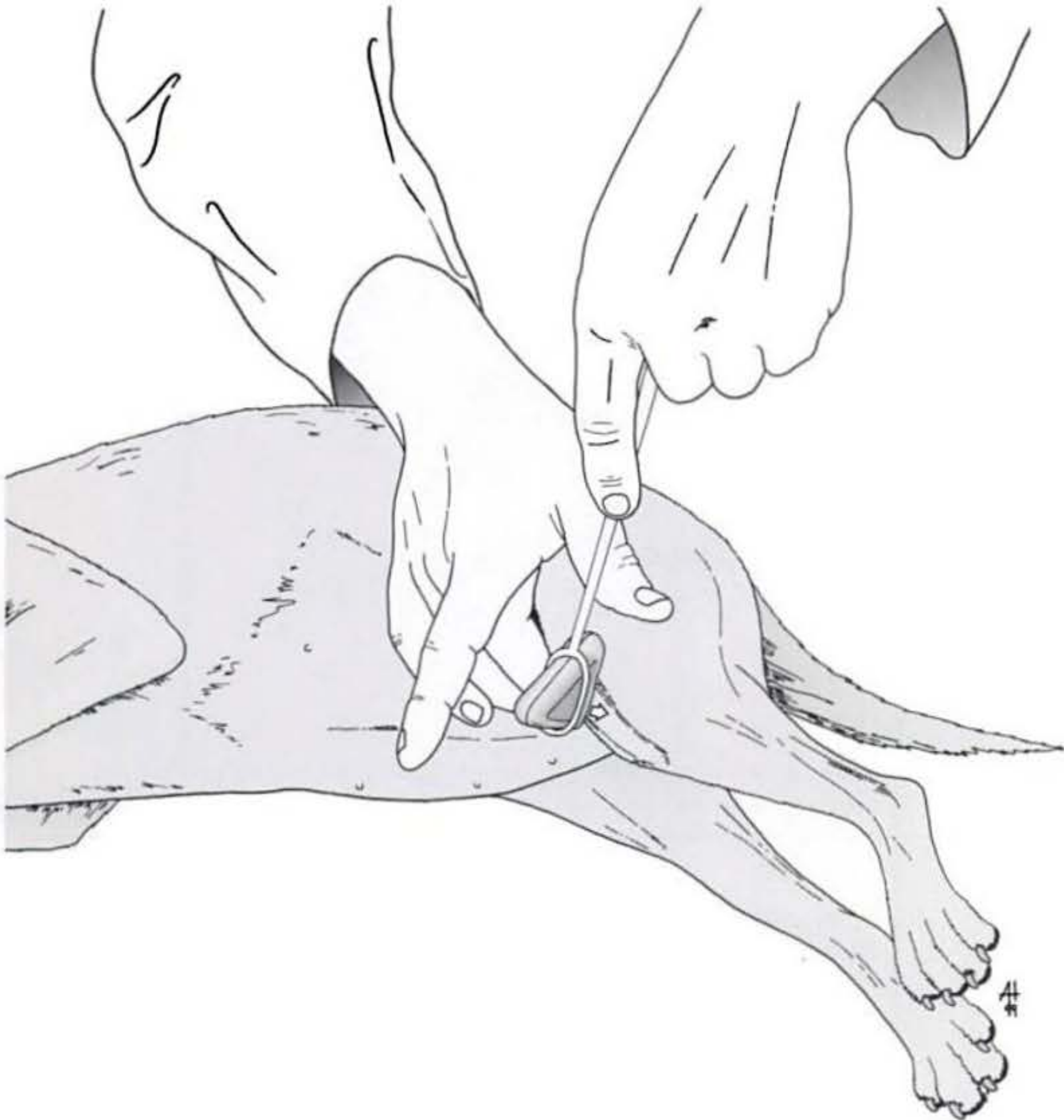


Fig. 2.13. The patellar reflex is elicited by percussing the patellar ligament between the patella and tibial tuberosity (Illustration by Anton Hoffman).

- b. The normal response is a single, quick extension of the stifle.
- c. The patellar reflex assesses the integrity of the femoral nerve and L4–L6 spinal cord segments.
- 6. Gastrocnemius reflex
 - a. Grasp the metatarsal area, extend the stifle, and flex the hock. Strike the common calcaneal tendon above the calcaneus (Fig. 2.14).
 - b. A normal response is contraction of the caudal thigh muscles.

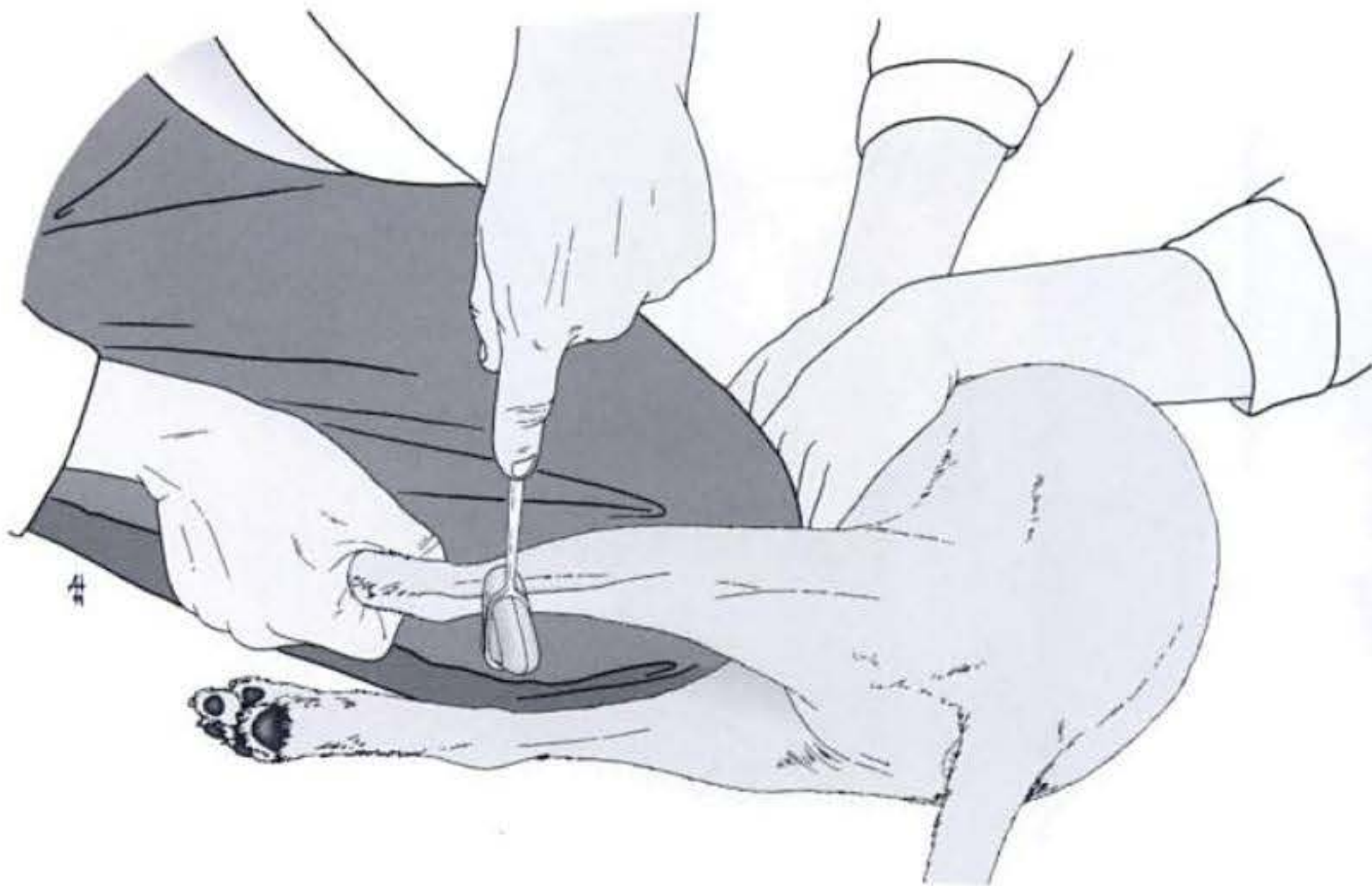


Fig. 2.14. The gastrocnemius reflex is elicited by percussing the gastrocnemius tendon proximal to the calcaneus (Illustration by Anton Hoffman).

- c. The recumbent leg tends to have a better response than the nonrecumbent leg.
- d. The gastrocnemius reflex assesses the integrity of the sciatic nerve and the L6–S2 spinal cord segments (primarily L7, S1 segments).
- e. The gastrocnemius reflex may be difficult to elicit in normal animals.
- 7. Biceps reflex
 - a. Grasp the antebrachium, extend the elbow (forelimb pulled caudally), and place your index finger on the tendinous insertion of the biceps on the radius. Lightly tap the dorsum of your finger (Fig. 2.15).
 - b. A normal response is contraction of the biceps brachii muscle. If this is difficult to appreciate (e.g., long-haired patient), let up with your left hand and observe for elbow flexion as you tap the tendon.
 - c. It is easier to test the recumbent leg.
 - d. The biceps reflex assesses the integrity of the musculocutaneous nerve and the C6–C8 spinal cord segments.
- 8. Triceps reflex
 - a. Grasp the antebrachium, flex the elbow, and rotate the shoulder medially (inward), so that the elbow joint is abducted. Strike the triceps tendon on the medial surface, above the olecranon (Fig. 2.16).

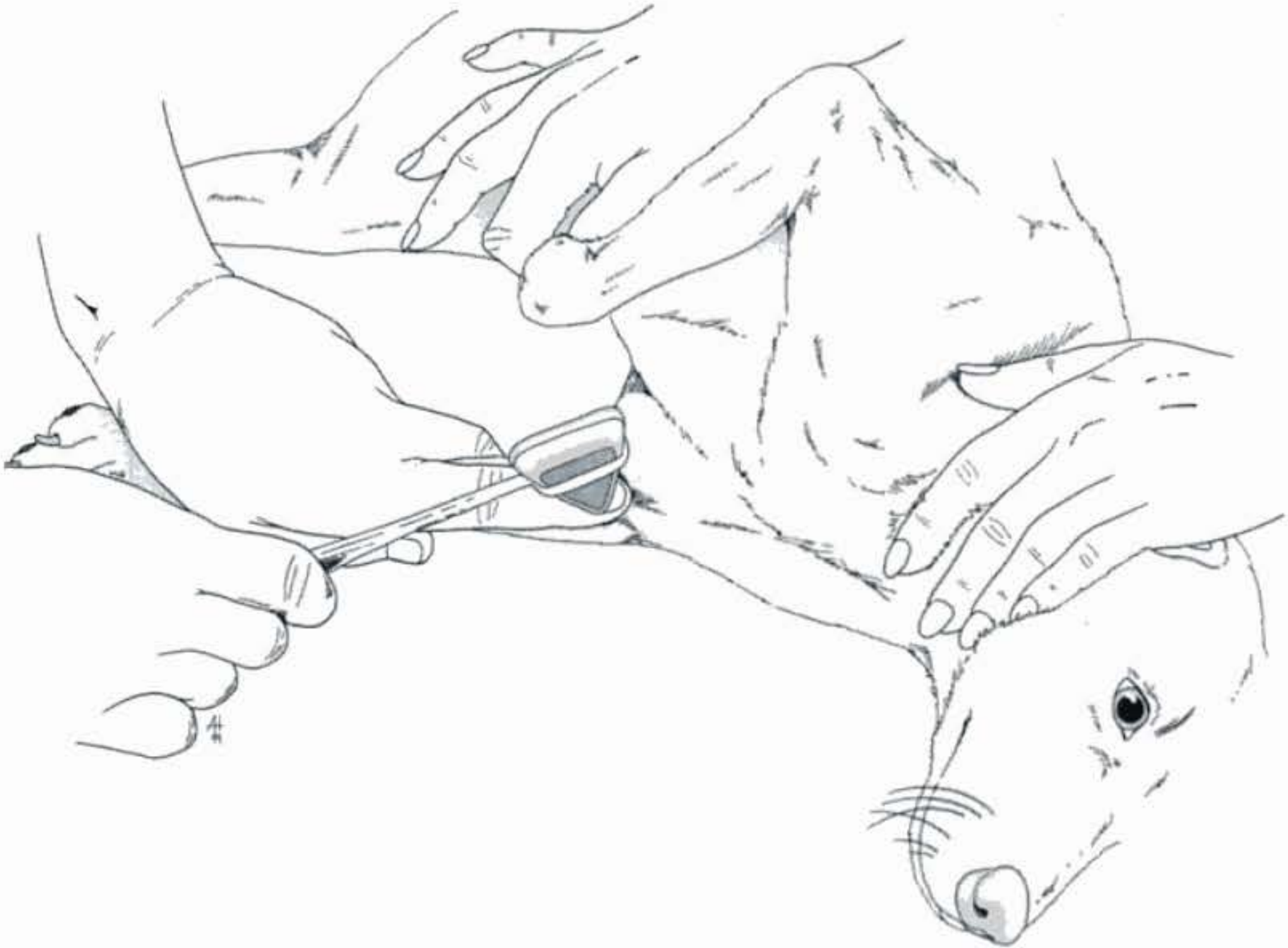


Fig. 2.15. The biceps reflex is elicited by striking the examiner's finger placed over the biceps tendon just proximal to the elbow (Illustration by Anton Hoffman).

- b. A normal response is contraction of the triceps muscle mass.
- c. The triceps reflex assesses the integrity of the radial nerve and the C7–T2 spinal cord segments.
- d. The triceps reflex may be difficult to elicit in normal animals.
- 9. Withdrawal (flexor) reflex
 - a. With the limb extended, pinch the interdigital skin lightly with your finger (Fig. 2.17).
 - b. The normal response is flexion of the hip, stifle, and hock (pelvic limb) and the shoulder, elbow, and carpus (thoracic limb).
 - c. If pain perception is intact, this may also elicit a behavioral response.
 - d. Observe the contralateral limb for extension (crossed-extensor reflex). A crossed-extensor reflex is abnormal in a recumbent animal and usually denotes UMN disease.
 - e. The withdrawal reflex assesses the integrity of spinal cord segments C6–T2 for the thoracic limb, and L6–S2 (primarily L7, S1) for the pelvic limb. The specific nerves that are assessed depends upon the specific area of skin stimulated (see Chapter 12 for autonomous zones). The efferent

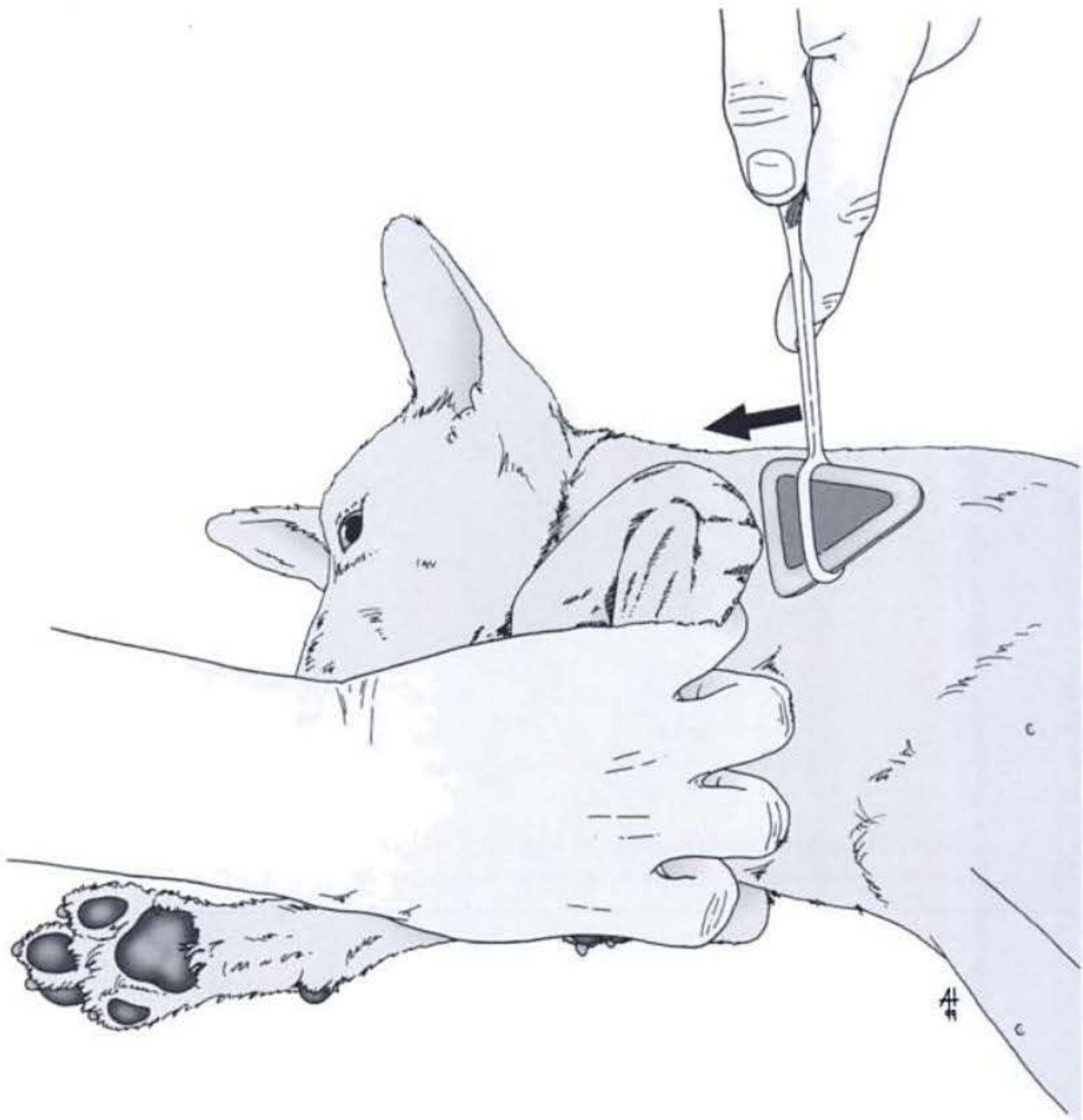


Fig. 2.16. The triceps reflex is elicited by percussing the triceps tendon just proximal to the olecranon (Illustration by Anton Hoffman).

arc of the thoracic limb withdrawal reflex is mediated by the musculocutaneous, axillary, median, ulnar, and radial nerves. In the pelvic limb, the efferent arc is mediated by the sciatic nerve.

10. Perineal (anal) reflex

- a. Lightly touch or stroke the perineum (Fig. 2.18). The left and right sides are tested.
- b. The normal response is contraction of the anal sphincter and tail flexion.



Fig. 2.17. The withdrawal reflex in the pelvic limb is tested by pinching the skin between the digits. Normal response is flexion of the hip, stifle, and hock. This is a reflex mediated at the level of the spinal cord and does not indicate conscious perception of pain (Illustration by Anton Hoffman).

- c. The perineal reflex assesses the integrity of sacral (S1–S3) and caudal (tail flexion) spinal cord segments, as well as perineal and pudendal nerve branches.
- 11. Cutaneous trunci (panniculus) reflex
 - a. With the patient standing or in straight sternal recumbency, lightly pinch the skin just lateral to the spine (Fig. 2.19). Start over the lumbosacral region and proceed cranially, one vertebral level at a time. The opposite side is tested similarly.
 - b. The normal response is a bilateral contraction of the cutaneous trunci muscle, resulting in a twitch of the skin over the thorax and abdomen. This reflex is present in the thoracolumbar region and is absent in the neck and sacral regions.
 - c. An obvious cutoff point suggests a spinal cord lesion 1–4 cord segments cranial to level of cutoff.
 - d. A lesion affecting the brachial plexus may cause a loss of the ipsilateral cutaneous trunci reflex with a normal response on the other side, regardless of the level at which the skin is stimulated.
 - e. The cutaneous trunci reflex assesses the integrity of the lateral thoracic nerve and C8–T1 spinal cord segments.

G. Palpation

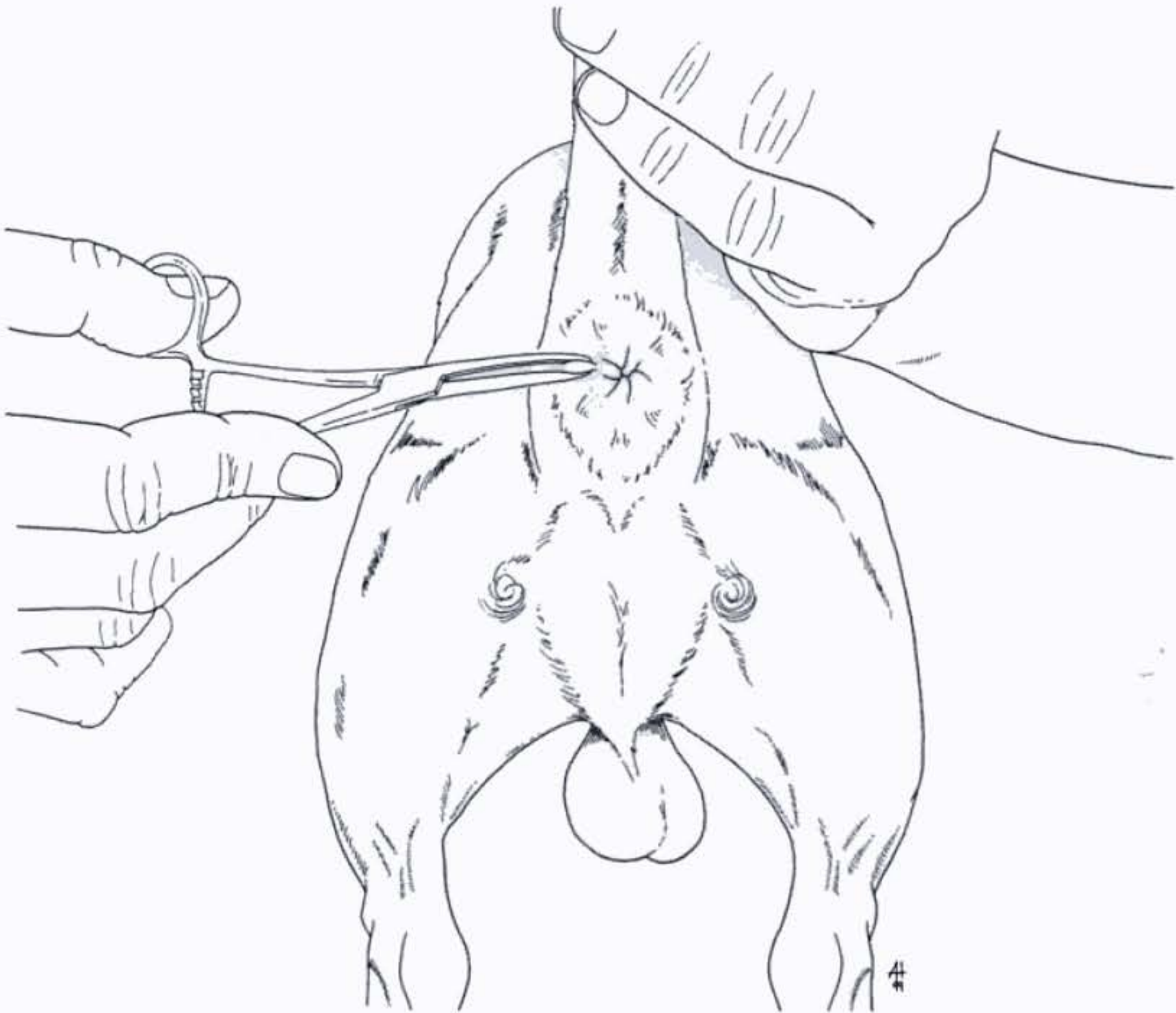


Fig. 2.18. Gently stroking or pinching the perineum tests the perineal reflex. The normal response is flexion of the tail and contraction of the external anal sphincter (Illustration by Anton Hoffman).

1. Light palpation helps detect swelling or atrophy.
2. Deep palpation and manipulation detect painful regions. If crying, whimpering, or muscle tensing occur on palpation, more vigorous maneuvers, such as manipulation, are unnecessary and may be dangerous in patients with unstable fractures or luxations. Also, palpation is usually more specific because manipulation of one region often produces movement in other areas.
3. Head
 - a. Check the calvarium for masses, defects, or persistent fontanelles.
 - b. After palpating the muscles of mastication, gently open the mouth to detect pain or reduced range of motion of the temporomandibular joints.
 - c. Retropulse the globe by gently pressing on the closed eyelids to detect pain or a retrobulbar mass.

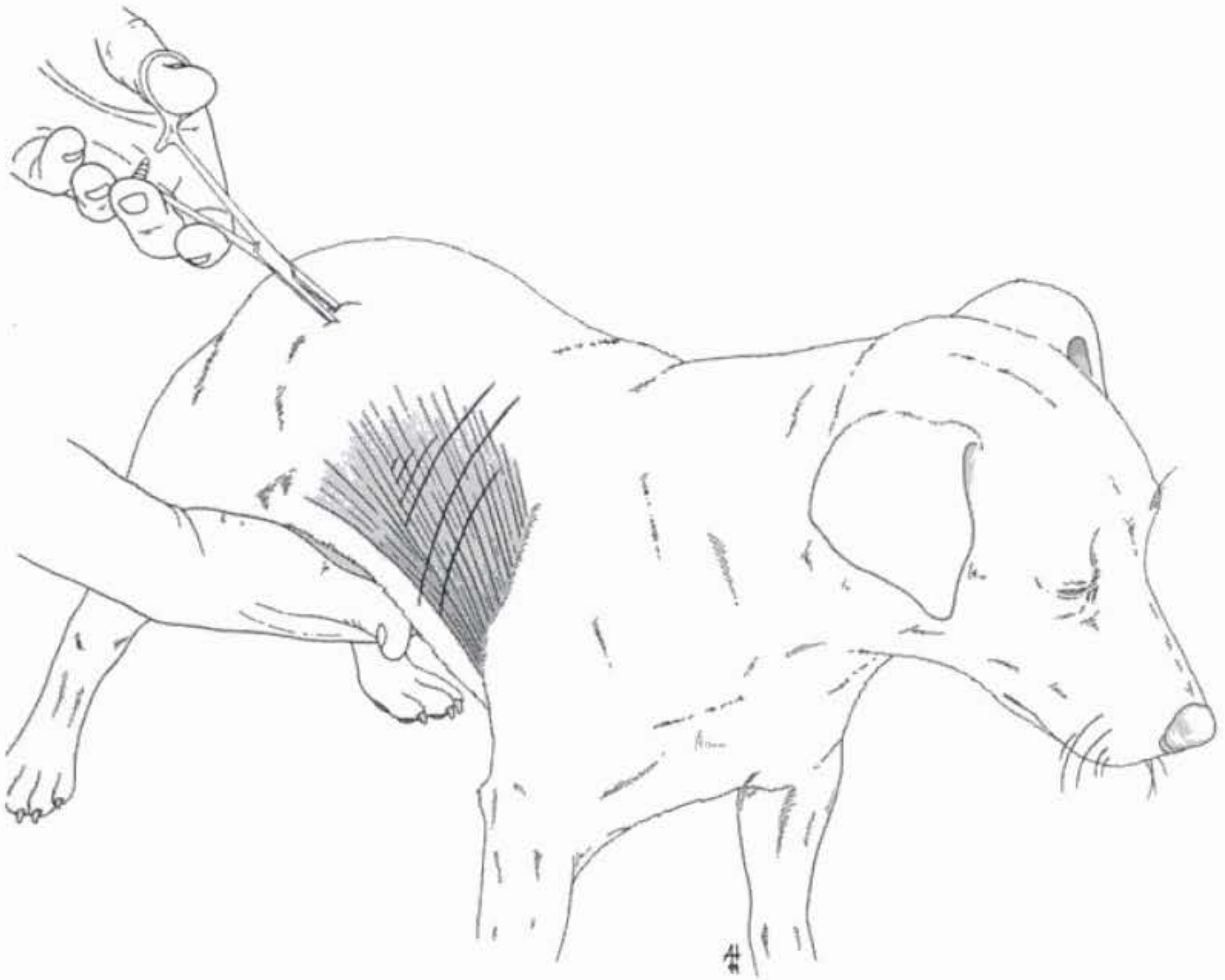


Fig. 2.19. The panniculus reflex is evaluated by lightly pinching the skin just lateral to the spine, starting over the lumbosacral region and proceeding cranially, one vertebral level at a time. The normal response is a bilateral contraction of the cutaneous trunci muscle resulting in a twitch of the skin over the thorax and abdomen (Illustration by Anton Hoffman).

4. Spine
 - a. Lightly palpate the spine to detect any curvature, displacement, atrophy, masses, or swelling.
 - b. Deeply palpate the paraspinal muscle for pain.
 - c. Palpate, extend, and flex the tail.
 - d. Downward pressure on the sacrum often elicits pain in animals with lumbosacral lesions.
 - e. When palpating the thoracolumbar spine, lightly place one hand on the abdomen to detect tensing of the abdominal muscles as the affected area is palpated.
 - f. The spinous processes, articular processes, and transverse processes or ribs are palpated separately.

- g. If palpation is not painful, the spine can be gently manipulated by applying ventral and lateral pressure to extend and flex the spine, respectively. To extend the lumbosacral joint, place one hand under the pelvis while the animal is standing. Raise the pelvis and press downward on the seventh lumbar vertebra with the other hand.
 - h. Cervical pain is often manifested by tensing of the cervical muscles and twitching of the ears during palpation or manipulation. If palpation does not induce pain, gently extend and flex the head with one hand while placing the other hand on the cervical muscles to detect muscle tensing. Caudal neck pain can often be detected by gently rocking the large transverse processes of the sixth cervical vertebra.
5. Limbs
- a. Limbs are initially palpated with the patient standing. Contralateral limbs are compared for symmetry.
 - b. The limbs are more closely examined with the animal in lateral recumbency, when the spinal reflexes are tested.
 - c. Palpate specific structures, not general regions. Carefully move overlying muscles to palpate bones without compressing adjacent structures. Palpate muscles without compressing or moving adjacent bones and joints.

H. Pain perception (nociception)

1. Superficial pain, also called fast pain, is sharp, well-localized pain most commonly originating in the skin.
 - a. With a hemostat, lift and grasp a small fold of skin at the test site. When the patient is quiet, gradually increase the force of the pinch until a response is elicited.
 - b. Two types of response may be seen:
 - (1) Reflex flexion of the limb or skin twitch indicating the sensory neurons and spinal segments are intact.
 - (2) A behavioral response, such as crying or biting, which indicates the ascending pain pathways in the spinal cord and brain stem to the fore-brain are intact.
2. Deep pain, also called slow pain, is felt as burning, aching, poorly localized pain originating from the skin or deeper structures.
 - a. The pathways that carry deep pain sensation are more resistant to damage than other pathways, including those responsible for proprioception, motor function, and superficial pain. Therefore, testing deep pain perception is necessary only if superficial pain is absent.
 - b. When there is no response to pinching with the fingers, use a hemostat to compress the digits or tail (Fig. 2.20). The degree of compression is gradually increased until a response is elicited.
 - c. Withdrawal of the limb indicates only an intact reflex arc (peripheral nerve and spinal segments). A behavioral response such as turning the head or vocalization indicates conscious perception.

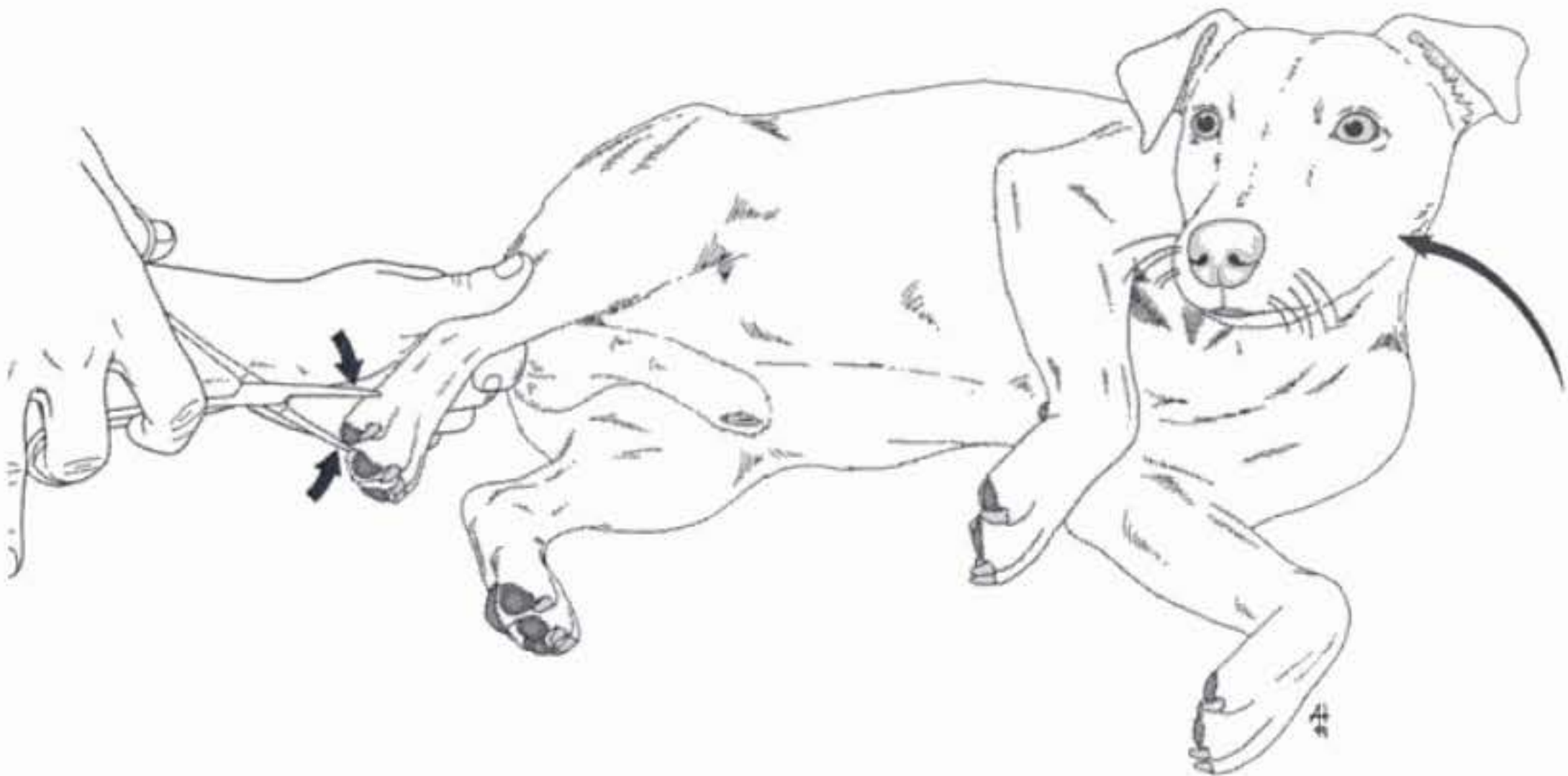


Fig. 2.20. Testing for deep pain perception is performed by using a hemostat to pinch the digit. A conscious response, such as crying or turning the head, indicates perception of deep pain (Illustration by Anton Hoffman).

- d. In patients with severe spinal cord injuries, the presence or absence of deep pain perception is important in assessing prognosis for recovery. It is critical not to confuse reflex withdrawal with conscious perception.

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Chapter 3

NEURODIAGNOSTICS

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I. Introduction

Once the neurologic examination is completed, a list of differential diagnoses is formed, based on the lesion localization, the signalment, and the history (e.g., onset, progression, painful vs. non-painful). In order to rule in or out the differentials on this list, additional diagnostic tests are often required. These might include: a minimum database (e.g., complete blood count, biochemistry panel, urinalysis); radiographs; cerebrospinal fluid (CSF) analysis; contrast radiographic studies, such as myelography or epidurography; advanced imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI); or electrodiagnostic studies, such as electromyography (EMG), nerve conduction velocity (NCV) studies, or brain-stem auditory evoked response (BAER) tests. Occasionally, muscle or nerve biopsy, or exploratory surgery is indicated. Diagnostic tests commonly used to evaluate dogs and cats with suspected neurologic disease are discussed in this chapter. For purposes of both patient safety and diagnostic accuracy, the procedures described in this chapter should be performed by appropriately trained individuals or under the direct guidance of such individuals. Most general small-animal practitioners will not be performing the procedures described in this chapter. However, maintaining a general knowledge base in regard to these procedures will assist the primary clinician in communicating effectively with both clients and specialists involved in managing patients with neurologic disease. The chapter is meant, therefore, to provide the reader with a brief overview of neurodiagnostic procedures; more in-depth descriptions of individual tests can be found by consulting the references at the end of the chapter.

II. Cerebrospinal Fluid (CSF) Analysis¹⁻¹⁶

The CSF bathes the brain and spinal cord. It is produced mainly by the choroid plexus of the lateral, third, and fourth ventricles, but also by brain capillaries, parenchymal cells, and ependymal cells. Carbonic anhydrase is an enzyme important in the formation of CSF; drugs that inhibit carbonic anhydrase may decrease CSF production. The normal rate of CSF production in dogs ranges from 47 to 66 $\mu\text{l}/\text{min}$, and in cats, 20–22 $\mu\text{l}/\text{min}$. The CSF is drained by the arachnoid villi, which are small projections of specialized arachnoid cells, into the venous sinuses that surround the brain. Abnormalities in the color, cellularity, and protein level of the CSF may contribute to or, in rare cases, confirm the diagnosis. It is rare for tumor cells or organisms to be visualized in CSF samples, but when it does occur, a definitive diagnosis can be made. The cell count and protein level of the CSF can be thought of as

the central nervous system analog of the CBC and serum protein level for the systemic circulation. Abnormal complete blood count (CBC) and serum protein results often assist in the diagnosis of systemic illness when viewed in the context of other laboratory abnormalities, as well as historical complaints and clinical findings; such abnormalities are typically not indicative of any specific disease when viewed as isolated test results. Similarly, results of CSF analysis often contribute to a diagnosis, but rarely by themselves provide a specific diagnosis. CSF analysis is very sensitive, in that it is often abnormal in patients with neurologic disease; it is very nonspecific, however, in most cases.

A. Indications for CSF collection (CSF “tap”)

1. Encephalopathies often are an indication for CSF analysis. In particular, infectious and noninfectious inflammatory diseases can be best characterized by evaluating the cellularity and protein levels in the CSF. Different inflammatory diseases lead to an accumulation of different types of cells in the CSF, and variably affect the amount and type of protein that is present. Degenerative, metabolic, traumatic, and neoplastic brain lesions may also alter the normal CSF. Any disease affecting the brain, including seizure disorders, should lead the clinician to consider CSF analysis as part of the diagnostic plan.
2. Any spinal cord lesion, or myelopathy, that is not readily diagnosed on plain radiographs, should be evaluated by CSF analysis. Focal, multifocal, and diffuse spinal cord lesions will lead to changes in the CSF. CSF collection should be done prior to myelography, since myelographic contrast agents will change the character of the CSF, and will frequently produce a mild inflammatory response. These changes are believed to influence CSF analysis for at least three to five days following the myelogram.
3. Lesions that affect the spinal nerve roots (radiculopathies) may be evaluated with CSF analysis. The meninges enclose the nerve roots distally until they become the peripheral nerves. Thus, any disease, especially inflammatory in nature, that affects the spinal nerve roots may alter the CSF.

B. Relative contraindications and risks of performing a CSF tap

1. Elevated intracranial pressure (ICP) due to mass lesions or inflammatory disease increases the risk of brain herniation (and subsequent death) when a CSF tap is performed. Typically, this is herniation of the cerebellar vermis and brain stem caudally through the foramen magnum. Cerebral herniation past the osseous tentorium caudally, or past the falx cerebri laterally may also occur. The incidence of brain herniation following a CSF tap has been found to be slightly higher in cats than dogs. Mannitol, corticosteroids, and hyperventilation may be used to decrease the risk. Because of the increased risk of herniation, CT or MRI should be performed prior to a CSF tap when mass lesions are suspected. There is probably no advantage of lumbar versus cerebellomedullary cisternal CSF collection in terms of brain herniation risk.

2. Inadvertant penetration of the parenchyma at the cerebellomedullary angle may lead to temporary signs of brain-stem disease, such as vestibular abnormalities, or cessation of voluntary respiration and death.
3. Performing CSF collection in small animals requires general anesthesia, as a rule. If the patient is an unacceptable anesthetic risk, lumbar puncture may be attempted with sedation and local (epidural) anesthesia.

C. Areas of CSF procurement and collection technique

1. One milliliter per 5 kg body weight of CSF can be safely removed at one time for analysis. Usually, 1 to 1.5 ml are collected (about ten drops). The fluid should be collected in a sterile glass tube, preferably without EDTA. EDTA may cause falsely elevated protein concentrations, as well as falsely low cell concentrations in small samples. Since EDTA is bactericidal, it may interfere with CSF culture results in cases of CNS bacterial infections.

Cerebrospinal fluid is most commonly obtained from the cerebellomedullary cistern (cisternal tap; Fig. 3.1). CSF collected from this site may be more representative of lesions involving the brain than CSF collected from a lumbar puncture. Anatomic landmarks useful in performing cisternal CSF taps include the external occipital protuberance, the cranial aspect of the dorsal spine of the axis (C2 cervical vertebra), and the transverse processes ("wings") of the atlas (C1 cervical vertebra). The patient is placed in lateral recumbency and the neck is flexed by an assistant. The animal's nose must be kept parallel with the table. A noncollapsing endotracheal tube should be used, to avoid occluding airflow during the procedure. The assistant should "tuck in" the animal's chin and push the external occipital protuberance toward the individual performing the tap. Placing some form of support under the neck (e.g., rolled up paper towel) will help keep the spine of the axis and the external occipital protuberance in line.

The skin in the region of the tap is shaved and aseptically prepared, and a 22-gauge spinal needle with a stylet (20-gauge is acceptable in larger patients) is inserted on midline, directed toward the occipitoatlantal space. Sterile gloves are worn for the duration of the procedure. The proper location for needle insertion can be estimated in several ways. The authors prefer to locate the cranial aspect of the C2 spine with an index finger, then press firmly with the finger tip as the finger is simultaneously advanced cranially. In most patients, a ridge or "divet" can be palpated approximately one-third of the distance between the cranial aspect of the C2 spine and the external occipital protuberance. This ridge is the cranial aspect of the arch of C1. Inserting the needle just cranial to the ridge should allow entry into the occipitoatlantal space. An alternative method is to draw an imaginary line across the cranial limits of the wings of C1 and a perpendicular line from the external occipital protuberance caudally. The needle can be inserted at the intersection of these lines. The skin is punctured first, then the index finger and thumb of one

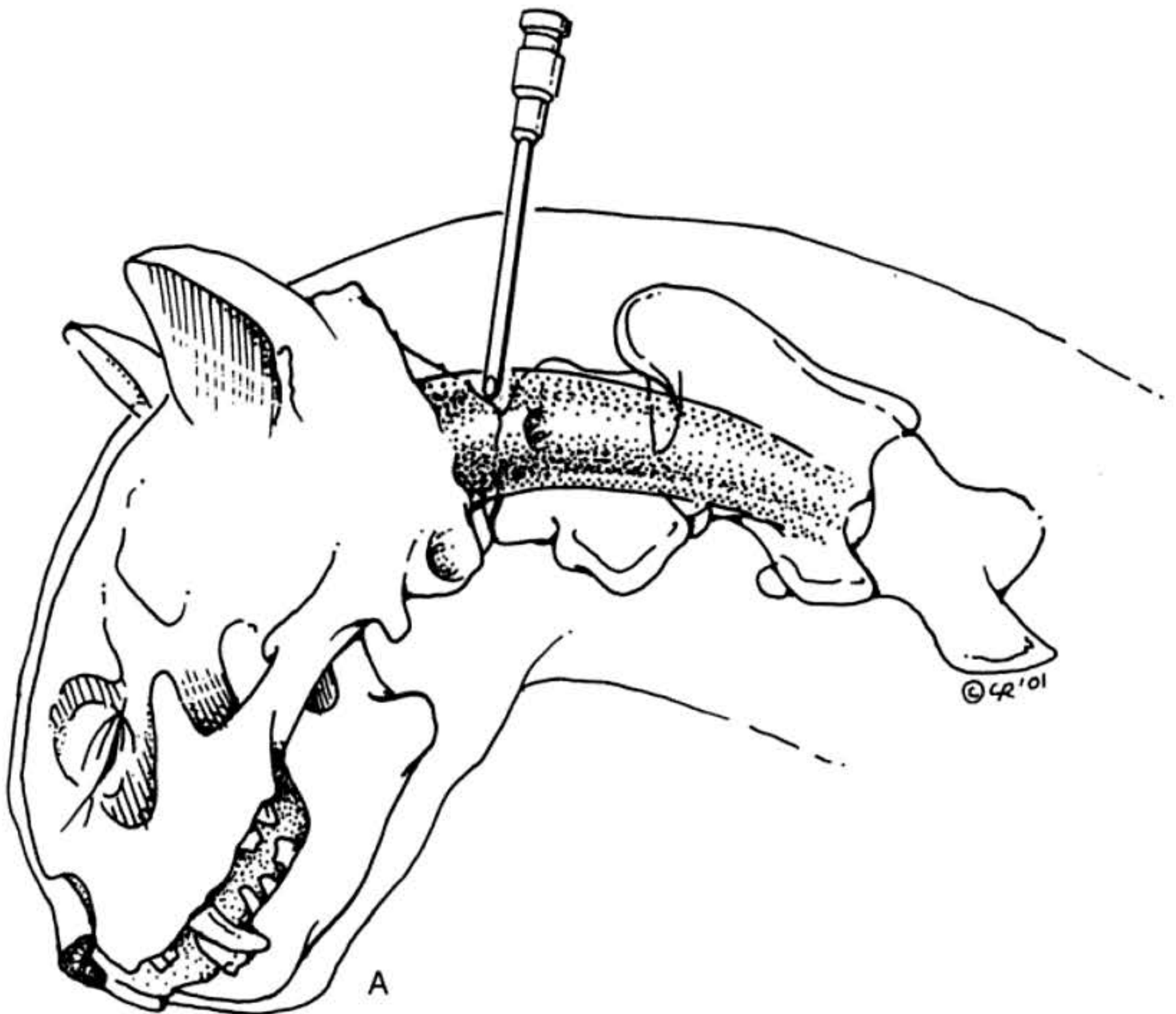


Fig. 3.1. Anatomic landmarks for cerebellomedullary cisternal CSF collection in the cat, lateral (A) and dorsoventral (B) views (Illustration by Carol Rudowsky).

hand (left hand for a right-handed person) is used to stabilize the needle against the skin surface, as the other hand is used to slowly advance the spinal needle. After every few millimeters of advancement, the stylet is removed to observe for CSF flow. Typically, the clinician will be able to feel the needle pass through fibrous tissue planes, producing a “popping” sensation. If the needle abuts bone, slight cranial or caudal redirection of the needle tip may allow entry into the dorsal subarachnoid space.

2. Lumbar puncture for CSF collection (lumbar tap) is usually performed at the L4/L5 space in large dogs or at the L5/L6 space in smaller dogs and cats (Fig. 3.2). Lumbar CSF may be more representative of lesions involving the thoracolumbar spinal cord than CSF from a cisternal puncture. The patient is placed in lateral recumbency and an area is shaved and aseptically prepared

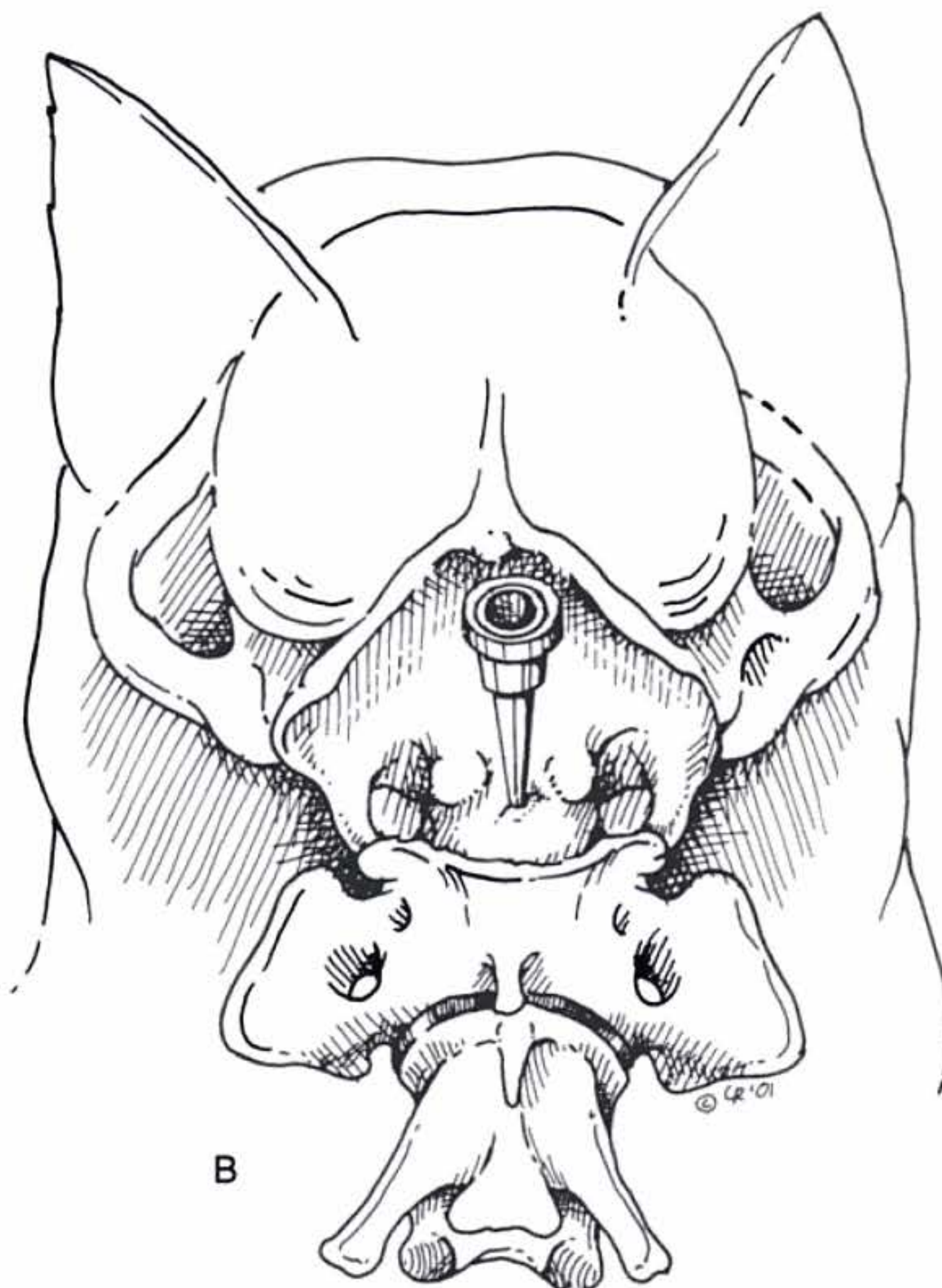


Fig. 3.1. Concluded.

for CSF collection. The patient's pelvic limbs are advanced cranially, in order to open up the interarcuate space. The authors prefer to face the ventral aspect of the patient, and bend over the patient to insert the spinal needle. The spinal needle is inserted just lateral to midline, adjacent to the caudodorsal limit of a spinous process (L6 for L5/L6 puncture; L5 for L4/L5 puncture). The needle is inserted at a 30°–60° angle from an imaginary line drawn perpendicular to the long axis of the spine.

After the interarcuate space is entered, the needle will pass through the dorsal dura mater. Often, at this point, a twitch of the pelvic limbs and/or tail will be noted. The needle is advanced to the floor of the vertebral canal, and

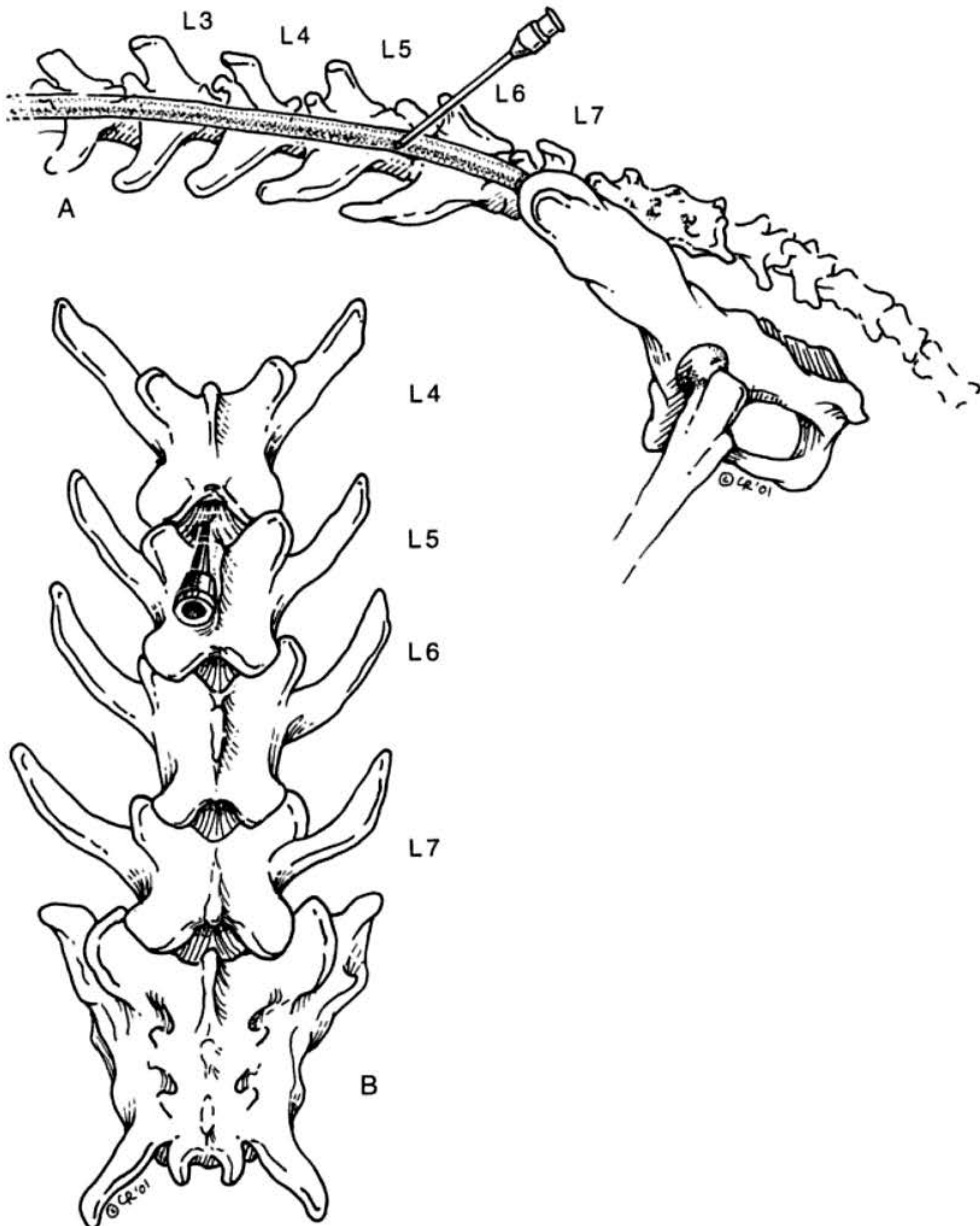


Fig. 3.2. Anatomic landmarks for obtaining CSF via lumbar puncture in the dog, lateral (A) and dorsoventral (B) views (Illustration by Carol Rudowsky).

the stylet is withdrawn. CSF is allowed to drip into a collection tube. Although the spinal needle penetrates the spinal cord during a lumbar CSF tap, this does not appear to cause any clinical problems.

D. CSF evaluation

There are a variety of tests that can be performed on CSF. Typically, a total cell count, differential cell count (after cytocentrifugation), and a protein level are ascertained. A glucose level is occasionally obtained, and is normally 60%–80% of the blood glucose level. If infectious disease is suspected, appropriate cultures or serology can be performed on the fluid. Electrophoresis of CSF may help to characterize the type(s) of protein present in the CSF. For some diseases (e.g., canine distemper virus), amplification of genetic material via polymerase chain reaction (PCR) may be indicated. Ideally, cell counts should be performed within 30 min of CSF collection; however, there is recent evidence that reliable cell counts may be obtained up to 48 hr later when the CSF is preserved through the addition of autologous serum. Prior treatment may alter the expected results of CSF analysis, especially in patients with inflammatory disease treated with corticosteroids.

1. Color and clarity

Normal CSF is clear and colorless, with the consistency of water. Prior hemorrhage (occurring a minimum of 10 hr prior to CSF collection) in the CSF may result in a yellow tinge, referred to as xanthochromia. This discoloration can persist for 2–4 wk following hemorrhage into the subarachnoid space, but is usually resolved by four to eight days. Other potential causes for xanthochromia are severe icterus, and markedly elevated CSF protein levels.

Gross blood contamination may be iatrogenic, or due to ongoing hemorrhage in the subarachnoid space. Iatrogenic hemorrhage is more common with lumbar taps, compared to cisternal taps. Although iatrogenic hemorrhage interferes with interpretation of CSF results, the extent to which it does so is controversial. It has been suggested that each 500 red blood cells (RBCs)/ μl in a hemorrhagic CSF tap may account for one white blood cell (WBC)/ μl in dogs, each 100 RBCs/ μl accounting for one WBC/ μl in cats. However, it has also been demonstrated that RBC counts in CSF as high as 15,000/ μl can occur with minimal elevation of the WBC count. The effect of hemorrhage on CSF protein levels is typically low, with approximately 1200 RBCs/ μl needed to increase the protein concentration by 1 mg/dl.

Increased turbidity of CSF is usually due to an elevated number of cells (over 200 WBCs/ μl , over 400 RBCs/ μl), and occasionally due to increased protein levels. Elevated protein levels in CSF will also cause the fluid to be more viscous. CSF that tends to clot is rare, and is caused by markedly increased amounts of protein.

2. Total and differential WBC count

Though the actual number may vary with the laboratory used, there are typically less than five nucleated cells/ μl of CSF. In normal dogs and cats, lumbar CSF typically has fewer WBCs/ μl than cisternal CSF. The distribution should be predominantly mononuclear cells with only occasional neutrophils.

3. Protein level

Quantitative determinations are the most accurate. Although each laboratory will establish normal ranges, normal protein concentration for cisternal CSF is less than 27 mg/dl in dogs and cats. Normal protein levels will be

higher when the CSF is collected from a lumbar puncture (approximately twice that of cisternal CSF, or less than 45 mg/dl).

E. CSF in disease

1. The greater the meningeal or ependymal involvement, in general, the greater the number of white blood cells (WBC) expected in the CSF. Deep-seated parenchymal lesions may be associated with mildly increased or normal cell counts, often with elevated protein levels. Increased nucleated cell counts in the CSF are referred to as *pleocytosis*. A normal cell count with an elevated protein level is often referred to as *albuminocytologic dissociation*.
2. Suppurative means a predominance of neutrophils. A neutrophilic pleocytosis is often associated with bacterial infections and corticosteroid-responsive (aseptic) meningitis. Other diseases in which neutrophils may predominate in CSF include some viral encephalitides (e.g., acute canine distemper infection, FIP meningoencephalitis in cats), fungal infections, meningiomas, and fibrocartilaginous embolic myelopathy (FCE). Neutrophils associated with infectious diseases (e.g., bacterial meningoencephalitis) are more likely to be degenerate than those that occur in noninfectious (e.g., corticosteroid-responsive meningitis) disorders.
3. Mononuclear cell pleocytosis refers to a predominance of either lymphocytes or macrophages in the CSF. This is the most common pleocytosis encountered, and is usually associated with granulomatous meningoencephalomyelitis (GME) in dogs. The necrotizing encephalitides (Pug/Maltese encephalitis, Yorkshire terrier encephalitis) are usually characterized by primarily lymphocytic pleocytosis. Lymphosarcoma involving the CNS may also be associated with a lymphocytic pleocytosis. A predominantly mononuclear pleocytosis can be caused by fungal, viral (e.g., canine distemper virus), protozoal, rickettsial, and chronic bacterial infections.
4. Eosinophilic pleocytosis is rare. It has been associated with aberrant parasite migration in the CNS, rabies virus, cryptococcal, protozoal, and protothecal infections. There is also a rare idiopathic condition called eosinophilic meningoencephalitis, which is characterized by a substantial proportion of eosinophils in the CSF.

III. Neuroimaging

The realm of neuroimaging typically includes survey ("plain") radiographs (e.g., skull, spine), myelography, epidurography, diskography, computed tomography (CT), and magnetic resonance imaging (MRI). General anesthesia is often recommended for survey radiography, and is required for contrast radiography (e.g., myelography, epidurography), as well as CT and MRI studies. On some occasions, ultrasonography is also helpful. Ultrasonography can be used in the diagnosis of hydrocephalus and for intraoperative imaging of brain tumors. Ultrasonography can also be used to guide brain biopsies.¹⁷⁻²⁰ Scintigraphy and angiography are no longer commonly per-

formed for veterinary neurodiagnosis due to the wide availability of CT and MRI and the higher-quality images these tools provide. However, rectal scintigraphy is often performed to diagnose portosystemic shunts.^{21–24} Occasionally, scintigraphy is used to evaluate esophageal function (e.g., patients with megaesophagus) and patency of surgically placed shunts in hydrocephalic patients.

A. Survey (“plain”) radiographs^{25–30}

1. The main use of survey radiography is as a rapid screening tool for obvious bony abnormalities. Soft tissue structures of the CNS are poorly visualized, if at all, with survey radiographs. A minimum of two views (e.g., lateral and ventrodorsal) is required.
2. Survey radiographs of the skull may reveal fractures and osseous neoplasia, or may suggest soft tissue or fluid densities in the nasal passages, sinuses, or middle ear canals. Appropriate positioning for skull radiographs requires general anesthesia. In general, CT is preferable to radiographs for most of these purposes.
3. Survey spinal radiographs in the nonanesthetized patient are often of questionable diagnostic quality due to poor patient positioning and patient movement. Obvious osseous tumors (Fig. 3.3), advanced diskospondylitis

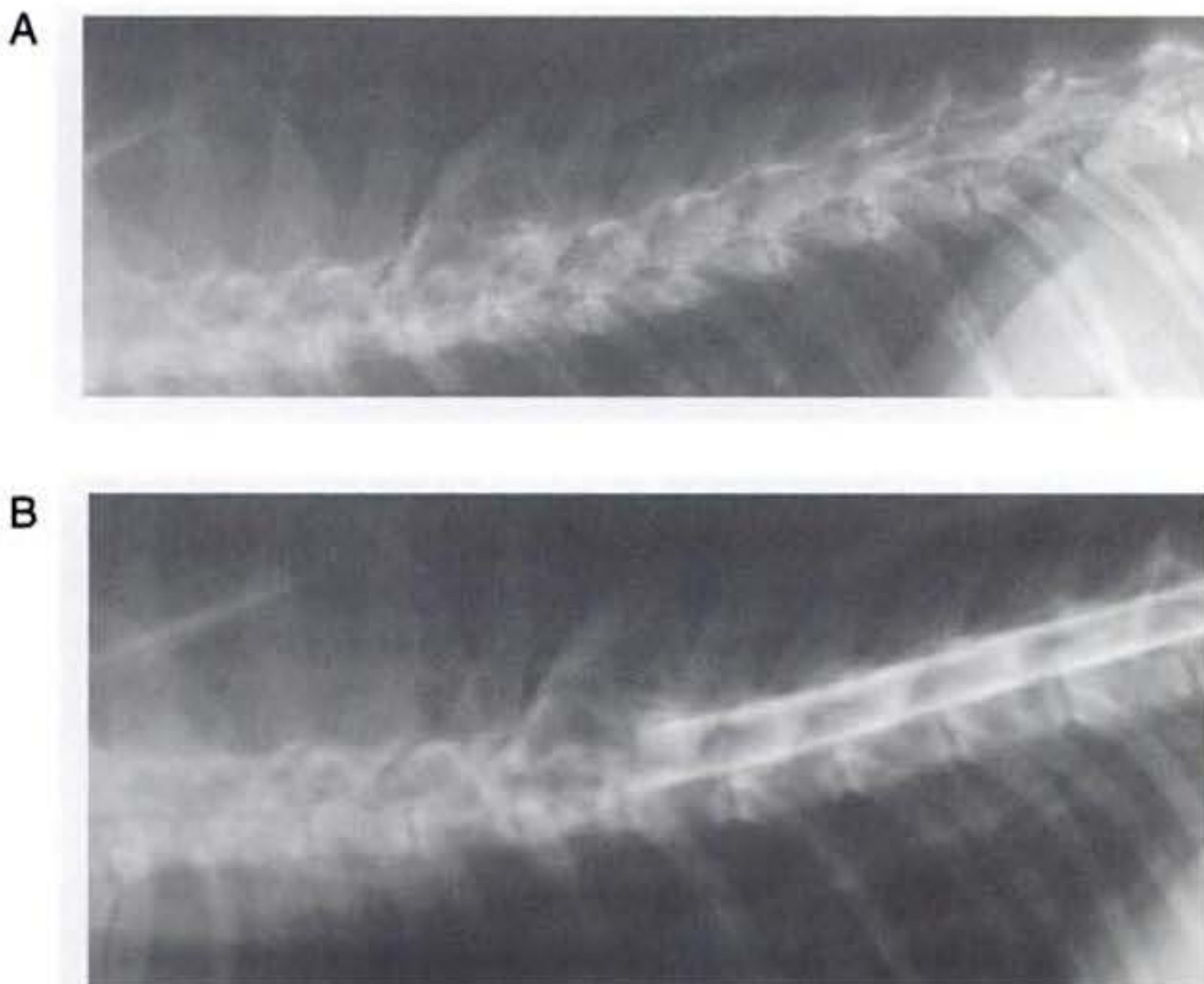


Fig. 3.3. Lateral radiograph of a cat's thoracic spine, before (A) and after (B) myelography. An abnormal fifth thoracic vertebra is evident. Osteosarcoma was confirmed after surgical decompression.



Fig. 3.4. Lateral thoracolumbar radiograph of a dog with advanced diskospondylitis.



Fig. 3.5. Lateral radiograph of a dog's spine with a traumatic luxation at the level of the T12 and T13 vertebrae.

(Fig. 3.4), displaced fractures or luxations (Fig. 3.5), and congenital vertebral anomalies (e.g., hemivertebrae), may be appreciated on survey spinal films in the unanesthetized patient. If the patient is likely to undergo anesthesia for myelography and/or surgery (e.g., acutely paralyzed Dachshund), performing survey radiographs on the unanesthetized patient is usually not justifiable.

4. High-quality spinal radiographs under anesthesia may reveal a number of abnormalities. In patients with intervertebral disk disease, collapsed disk spaces, decreased size of the intervertebral foraminae, or mineralized disk material within the vertebral canal or intervertebral foraminae may be appreciated (Fig. 3.6). Subtle vertebral fractures or subluxations with minimal displacement may be more readily apparent on radiographs performed with the patient anesthetized versus radiographs procured when the patient is awake. Other radiographic abnormalities that may be more evident in the anesthetized patient include subtle bony lesions associated with neoplasia (e.g., mild bone lysis), abnormalities associated with articular facets (including small fractures), and subtle bony changes suggestive of early diskospondylitis (e.g., small regions of vertebral end plate lysis). In general, survey radiography is less sensitive than CT for identifying subtle bone lysis and small fractures.

B. Myelography²⁵⁻³⁶



Fig. 3.6. Lateral thoracolumbar radiograph of an anesthetized dog with acute thoracolumbar disk extrusion. A collapsed disk space, decreased size of the intervertebral foramen, and calcified material in the vertebral canal are apparent at the L1/L2 intervertebral disk space.

1. Myelography is a procedure in which spinal radiographs are obtained following the injection of a radiopaque contrast agent into the subarachnoid space. Nonionic, iodinated, water-soluble contrast agents are used, iohexol and iopamidol being the most common.
2. The myelogram is performed via a cisternal or lumbar tap. CSF should be collected prior to contrast injection, as the contrast will change the composition of the CSF and prevent accurate analysis for a minimum of three to five days. The authors prefer lumbar versus cisternal injection of contrast, regardless of the area of interest. Lumbar myelography often results in better image quality, and is safer than cisternal myelography. The dosage of contrast used for a regional study (e.g., cervical myelogram with cisternal contrast injection) is 0.3 ml/kg body weight. For full studies (e.g., cervical myelogram with lumbar injection), the dose is 0.45 ml/kg body weight. The contrast is injected slowly, approximately 2–3 ml per minute. The authors prefer to administer a test injection (e.g., 0.5–1.0 ml, depending on patient size) to ensure the contrast is in the subarachnoid space, before administering the remainder of the calculated contrast dose.
3. Myelography is used to assist in the diagnosis of myelopathies. It is indicated for cases in which survey radiographs are either normal or inconclusive, despite neurologic evidence of myelopathy. Myelography is also often helpful in estimating the location, extent, and severity of spinal lesions. The ability to easily and rapidly visualize the entire spinal cord is an advantage of myelography over other imaging procedures (e.g., CT, MRI). Myelography is also generally less costly and more readily available than CT or MRI.
4. Despite the advantages of myelography, it is a somewhat invasive procedure and is associated with a low level of inherent risks. Overall, postmyelographic seizures occur in approximately 10% of dogs undergoing the procedure; this appears to be considerably more common in larger dogs (more than 29 kg). The incidence of seizures may be increased with cisternal contrast injection. Male Doberman pinschers with caudal cervical spondylomyelopathy, or

CCSM ("wobblers" syndrome), may be particularly predisposed to postmyelographic seizure activity. Most patients that seizure will do so only once or twice in the 24 hr following the procedure, and the seizures usually cease with intravenous diazepam injection (0.2–0.4 mg/kg). Maintaining slight elevation of the patient's head during and after the procedure (until the patient is awake) and assuring hydration with intravenous fluids during and 24 hr after myelography are recommendations to limit the occurrence and severity of postmyelographic seizure activity.

All dogs receiving a myelogram should be under close hospital observation (e.g., in an ICU) for the first 24 hr following the procedure. Parenchymal damage from insertion of the needle is rare in myelography, but may occur, especially in the cervical region. Worsened neurologic status postmyelogram is usually caused by transient chemical myelitis secondary to contrast injection. The risk for this may be higher in patients with preexisting inflammatory disease, or chronic spinal cord compression (e.g., chronic Type II disk disease). In the authors' experience, the risk of transient neurologic worsening appears to be highest in dogs with CCSM. These dogs typically regain premyelogram neurologic status within 72 hr. Inadvertant contrast injection into the parenchyma or the central canal of the spinal cord may cause worsened neurologic status. In most cases, patients recover from this iatrogenic trauma, but permanent deficits may occur in a small proportion of animals. Myelography is contraindicated for patients with known or highly suspected inflammatory disease of the central nervous system, as it may cause worsened neurologic status.

Myelography is also contraindicated in patients that may have elevated ICP. Since cervical hyperesthesia occasionally is associated with forebrain lesions, any historical or clinical indication of an underlying encephalopathy should prompt consideration of an alternative imaging modality (e.g., CT or MRI).

5. There are four basic myelographic patterns: normal, extradural, intradural/extramedullary, and intramedullary (Fig. 3.7). Normally, the contrast columns parallel each other and conform to the vertebral canal, except at the cauda equina region, where the subarachnoid space tapers. The spinal cord ends at about the L6 vertebral region in most dogs and at the first sacral vertebral region in most cats, although there may be quite a bit of variation between breeds.

The spinal cord is normally wider at the cervical and lumbosacral intumescences. The ventral subarachnoid space is often less prominent than the dorsal subarachnoid space in the thoracolumbar region in dogs. The dorsal subarachnoid space in the atlantoaxial region is often wider than the remainder of the spinal cord. The cervical spinal cord region in cats often appears wider on myelography, in comparison to dogs. A normal myelographic pattern is often associated with degenerative myelopathy and fibrocartilagenous embolic myelopathy (FCE). A normal myelogram may also occur with inflammatory myelopathies.

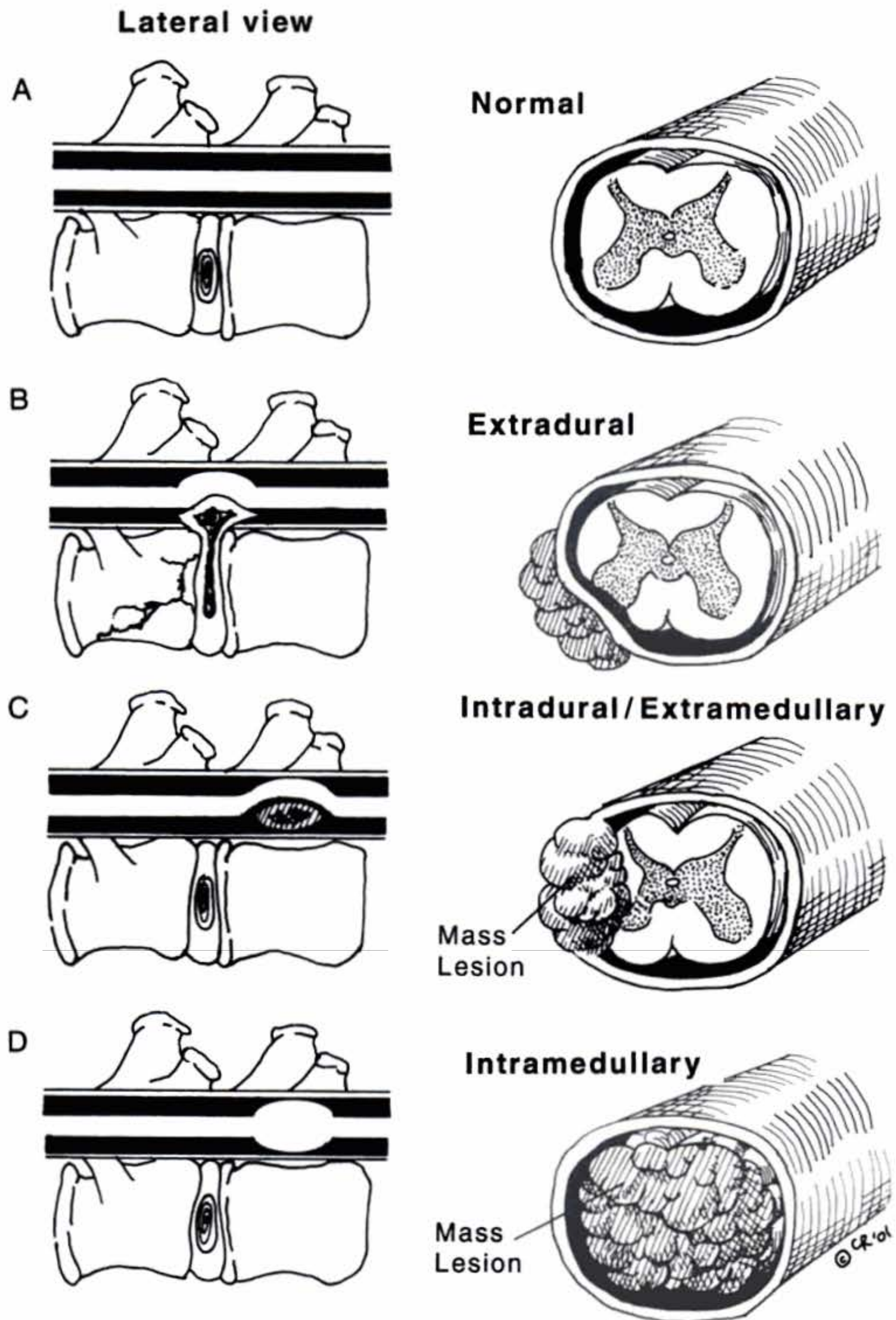


Fig. 3.7. Four basic myelographic patterns: (A) Normal, (B) Extradural, (C) Intradural/extramedullary, (D) Intramedullary (Illustration by Carol Rudowsky).

Intervertebral disk extrusion/protrusion is the most common cause of an extradural myelographic pattern. Other causes of extradural patterns include vertebral fracture/luxation, congenital vertebral anomalies, hypertrophied soft tissue structures (e.g., interarcuate ligament, synovial membranes), extradural hemorrhage, vertebral neoplasia, and soft tissue neoplasia (e.g., feline lymphosarcoma). It is important to realize that the nature of an extradural compression is best appreciated when viewed tangential to the direction of the cord deviation. For example, if a disk extrusion is compressing the cord from ventral to dorsal, with no lateralizing component, the myelographic pattern as viewed from a ventrodorsal view (parallel with direction of compression) could be misinterpreted as intramedullary.

An intradural/extramedullary pattern is produced when there is a lesion within the subarachnoid space (intradural), but not invading the parenchyma of the cord (extramedullary). As the contrast flows around the obstructive lesion, it may be outlined, appearing as a “filling defect.” Sometimes, the filling defect is incompletely outlined, and resembles a golf tee, hence the term “golf tee sign” (Fig. 3.8). Intradural/extramedullary patterns are most often associated with neoplasia, primarily meningiomas and nerve sheath tumors. Much less commonly, intradural hemorrhage may lead to this myelographic pattern. Intradural/extramedullary lesions may produce enough spinal cord swelling that contrast is excluded from the region of the mass. In such cases, the myelographic pattern may appear to be intramedullary. In such cases, a CT is often performed through the abnormal region, as contrast is better visualized on CT images.

An intramedullary pattern is typically associated with spinal cord edema, expansile parenchymal masses, or intraparenchymal hemorrhage. Differential diagnoses include FCE, neoplasia (e.g., astrocytoma, lymphosarcoma), inflammatory disorders (e.g., GME in dogs, FIP in cats), and trauma (e.g., hemorrhage and edema).

C. Epidurography^{26,31,37-43}

Myelography is often inadequate for the evaluation of cauda equina lesions in dogs because the subarachnoid space ends at the conus medullaris, which is in the L6 region in most canine patients. Epidural contrast injection may help



Fig. 3.8. Myelographic appearance of a “golf tee sign” (lateral view), indicative of an intradural/extramedullary lesion.

delineate compressive cauda equina lesions, particularly those at the L7/S1 intervertebral disk space (e.g., degenerative lumbosacral stenosis). Epidurography is associated with a low level of morbidity. Due to the irregular contour of the epidural versus subarachnoid space, the contrast columns of an epidurogram appear comparatively rough and uneven in comparison with the contrast columns of a myelogram.

Iohexol or iopamidol is used. The volume of contrast to inject is 0.1–0.2 ml/kg body weight. After aseptic preparation of the chosen site, injection of contrast material may be performed at L7/S1, at the sacrocaudal junction, or between one of the caudal intervertebral spaces. The disadvantage to L7/S1 contrast injection is that injection artifact may produce an unsatisfactory epidurogram in some cases.

Multiple radiographic views are helpful. These include lateral films taken with the coxofemoral joints in neutral, flexed, and hyperextended positions. In a normal epidurogram, contrast fills the epidural space evenly with the pelvis in any position.

Potential abnormalities that may be appreciated on an epidurogram include complete obstruction of cranial flow of contrast media past the L7/S1 space, or dorsal deviation of the ventral contrast column over this space (Fig. 3.9). This deviation may be exacerbated on extended views, and alleviated on flexed views. Occasionally, ventral deviation of the dorsal contrast column may be appreciated.

D. Diskography^{26,38,40,41,43}

1. Diskography is used less often than epidurography for evaluation of L7/S1 disk lesions. Similar to epidurography, this procedure is associated with a low level of morbidity. Diskography involves injecting iohexol or iopamidol (0.1–0.3 ml/kg body weight) directly into the nucleus pulposus of the disk, after which radiographs are procured.



Fig. 3.9. Lateral view of an epidurogram in a dog with degenerative lumbosacral stenosis. There is a ventral extradural compressive lesion at the L7/S1 intervertebral disk space. There is also evidence of diskospondylitis at this site.

2. After aseptic site preparation, the spinal needle is placed directly into the L7/S1 disk, preferably under fluoroscopic guidance. In a normal disk, it is very difficult to inject contrast. In a degenerative disk, 2–3 ml of contrast is often readily injected in a large breed dog. Compression of the cauda equina region by the contrast-delineated L7/S1 disk is often readily evident (Fig. 3.10).
3. The authors prefer to perform a combination diskography/epidurography procedure using a single needle puncture. After the diskogram is performed, the needle is withdrawn from the disk into the epidural space, and additional contrast is injected. Additional radiographs are then obtained after the epidural contrast is administered (Fig. 3.11).

E. Computed tomography (CT)^{25,26,30,42,43–52}

1. In computed tomography, X rays and computers are used to provide cross-sectional images of the patient. The final images are comprised of many small image squares called pixels. The thickness of these image squares (voxels) is determined by the chosen image thickness. The patient is placed in the opening of the CT gantry (Fig. 3.12). The gantry contains the X-ray tube, X-ray



Fig. 3.10. Diskogram (lateral view) from a dog with a compressive disk lesion at L7/S1.



Fig. 3.11. Combined diskogram/epidurogram (lateral view) from a dog with degenerative lumbosacral stenosis.



Fig. 3.12. Patient in the gantry of the CT machine.

collimators, and X-ray detectors. The X-ray tube and detectors are on opposite sides, and the patient is between them. Slice thickness is controlled by the collimators. The X-ray tube rotates around an object of interest as X rays are emitted. As the X-ray beam passes through an object, it is attenuated by tissues in its path. Each tissue attenuates the beam to a different degree. The different attenuating abilities of different tissues, or linear attenuation coefficients, provide the basis of tissue contrast. The attenuated beam of X-ray photons is received by the detector and the information is fed into the computer. The computer assigns gray scale numbers (Hounsfield units) to the tissues that the X-ray beam passed through, based upon their linear attenuation coefficients.

2. The resultant image reflects the different gray scale numbers of different tissue types, and therefore their respective abilities to attenuate X rays. As one would expect from conventional X-ray procedures, bone appears white, air appears black, and fluid is somewhere in between (gray). The corresponding Hounsfield numbers for these tissues are +1000, -1000, and 0, respectively.
3. The human eye can discern approximately 20 shades of gray. The number of shades of gray in the image, as well as the central gray color (above which tissues are brighter, below which they are darker) can be manipulated once the image information is received by the computer. Choosing the central gray color, above which tissues appear brighter, and below which darker, is referred to as setting the *window level (WL)*. The Hounsfield unit of the tissue of interest is typically chosen as the center of the window level. The number of shades of gray assigned to a particular image represents the *window width (WW)*. A narrow window width is chosen for soft tissue (e.g., brain parenchyma) in order to improve contrast resolution (the ability to discern differences in composition of tissues in close proximity). A wide window width is chosen for tissues in which good inherent contrast already exists

(e.g., air in the frontal sinus region), or when imaging a region where a wide range of tissue densities is displayed (e.g., bone/brain parenchyma interface). When imaging brain parenchyma, a WL of approximately 35 and a WW of 150 may be assigned (Fig. 3.13). In contrast, when imaging bony tissue, a WL of 420 and WW of 1500 may be used (e.g., a *bone window*; Fig. 3.14).

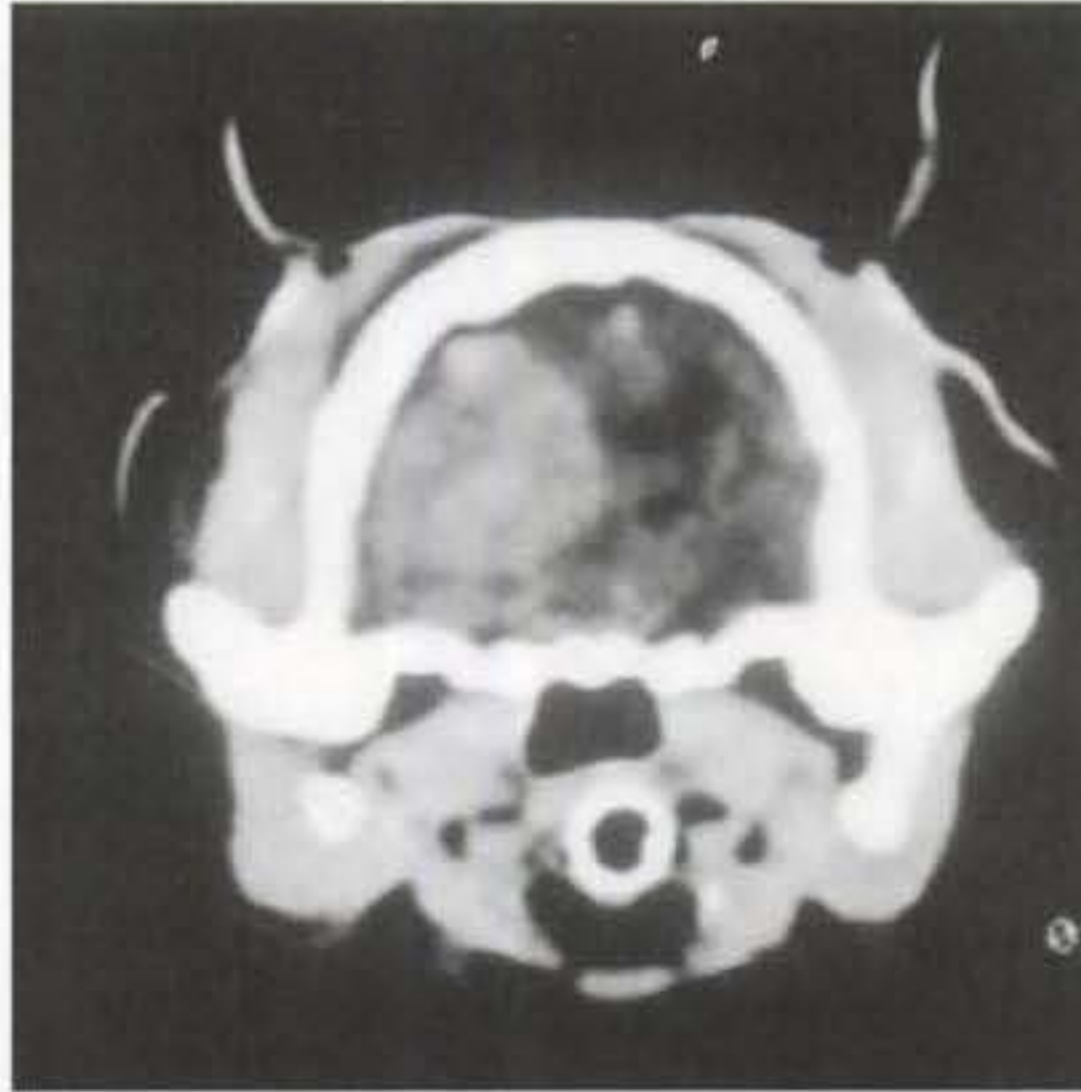


Fig. 3.13. CT image of an intracranial meningioma in a cat (transaxial view), using a soft tissue window.



Fig. 3.14. CT image of a multilobular osteochondrosarcoma of the skull in a dog (dorsal view), using a bone window.

4. After obtaining CT scans of the brain, contrast is often given intravenously and the patient is rescanned. The contrast agent (iodinated, e.g., meglumine iodine) will often demonstrate areas of blood-brain barrier disruption (Fig. 3.15).
5. With appropriate computer software, tissue voxels can be combined to produce a three-dimensional image (3-D reconstruction; Fig. 3.16) or to produce images in other planes.
6. Computed tomography is most often used to help diagnose brain disorders. Computed tomography is also occasionally used in cases of spinal disorders, often in conjunction with myelography (Fig. 3.17). Disorders of the cauda equina (e.g., degenerative lumbosacral stenosis) are also effectively imaged by CT.
7. Advantages of CT over other imaging modalities are numerous. Computed tomography provides superior soft-tissue contrast in comparison with conventional radiography. The cost of CT is typically less than magnetic resonance (MR) imaging. Computed tomography is a more rapid imaging modality than MRI, and bone and acute hemorrhage are better visualized with CT versus MRI; these attributes make CT preferable to MRI in acute head trauma patients. Other advantages of CT imaging are the ability to alter window settings after data acquisition and the ability to form 3-D reconstructed images.
8. There are several disadvantages of CT compared to MR imaging. Computed tomography involves exposure to ionizing radiation (X rays) whereas MR

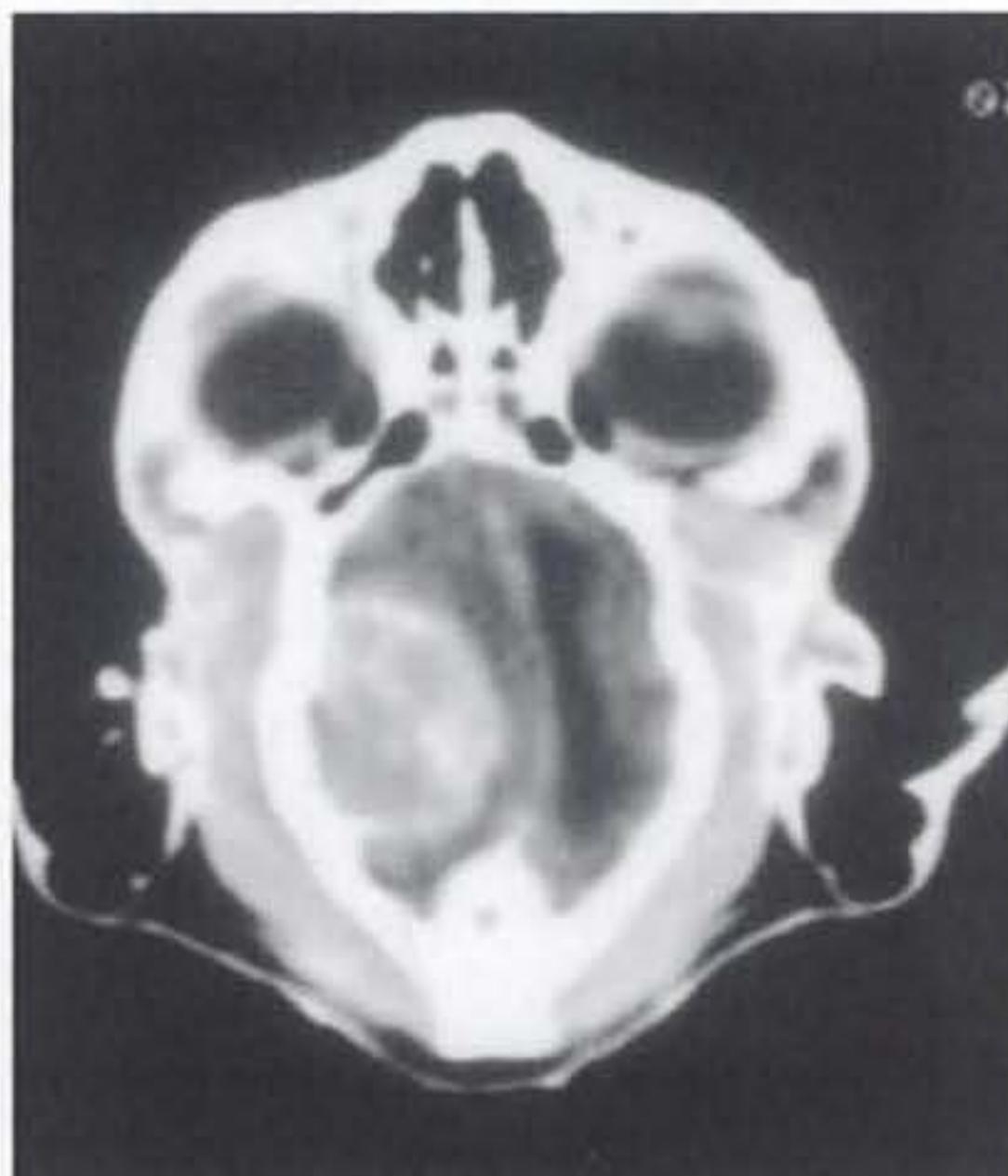


Fig. 3.15. CT image of the cat's brain in Figure 3.13 (dorsal view) following intravenous administration of contrast.



Fig. 3.16. Three-dimensional reconstructed CT/myelographic image of a comminuted thoracic vertebral fracture in a dog.



Fig. 3.17. Combined CT/myelogram image (transaxial view) from a dog with a spinal arachnoid cyst (Courtesy of Dr. Mike Walker).

imaging does not. Magnetic resonance imaging provides superior soft tissue detail in comparison with CT. Computed tomography is usually adequate for visualizing mass lesions in the brain and spinal cord. However, subtle parenchymal lesions (e.g., inflammatory foci in GME) as well as brain (especially brain-stem) and spinal cord lesions in very small dogs and cats may be more appreciable on MRI than CT. Image artifacts are typically more of a problem with CT imaging versus MR imaging. In particular, *beam hardening*, which appears as black streaks, is a common CT artifact when imaging the caudal fossa (Fig. 3.18). This artifact is due to the dense bone in the petrous

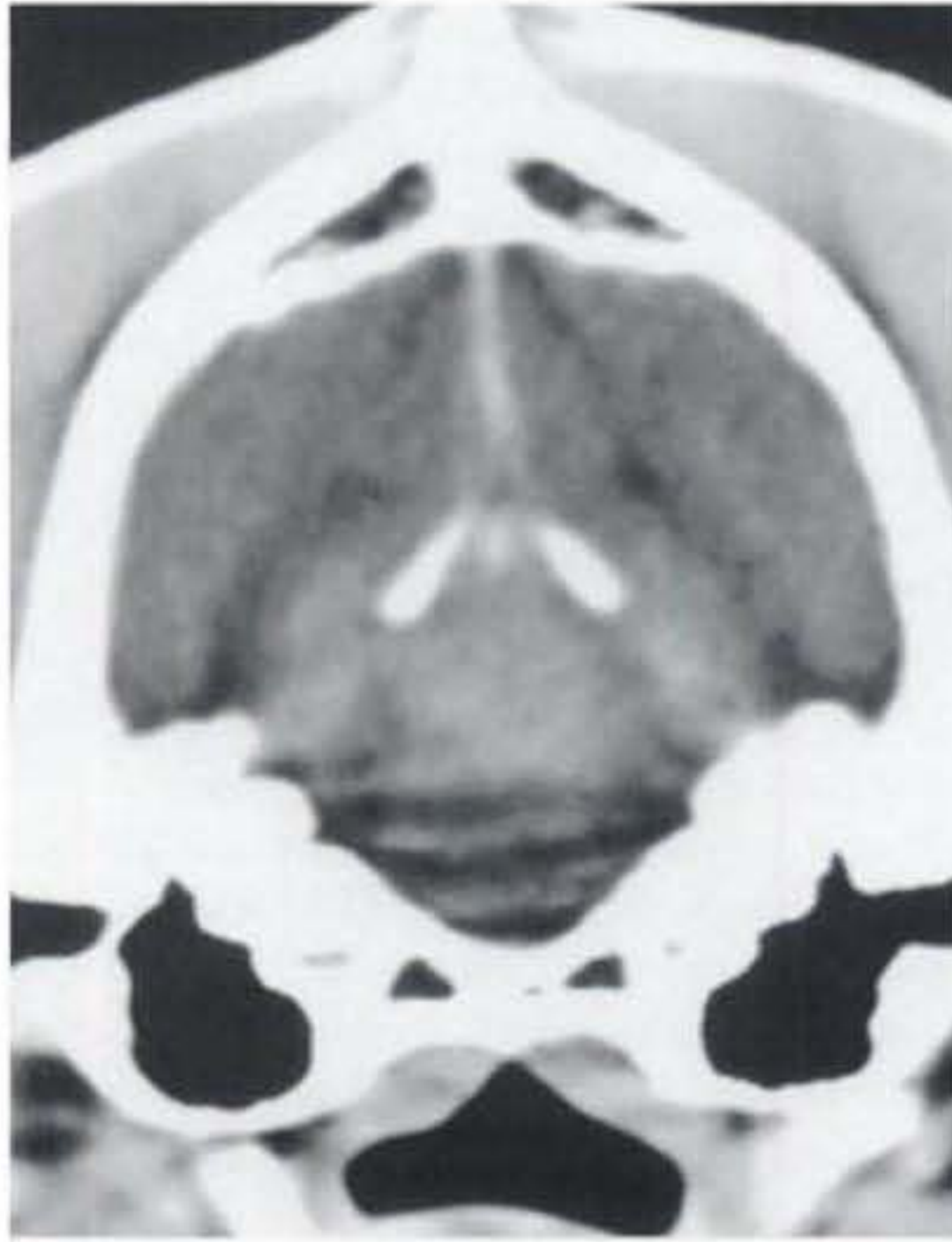


Fig. 3.18. Transaxial CT image of the caudal fossa of a dog, demonstrating beam hardening artifact in the brain-stem region (Courtesy of Dr. Mike Walker).

temporal region. The average energy of the X-ray beam that traverses this thick bone and reaches the detectors is very high, because photons of lower energy are absorbed by the bone. The computer interprets the high average energy beam as X rays that have passed through a low-density structure, incorrectly assigning the tissue a low Hounsfield unit number (black streaks). Beam hardening does not occur in MR imaging.

F. Magnetic resonance imaging (MRI)^{25,26,30,46,53-64}

1. Magnetic resonance imaging is based upon the magnetic properties of living tissue, primarily protons of hydrogen atoms. The proton has a spin and a charge, and therefore produces a tiny magnetic field. Each proton behaves as a tiny dipole or compass needle. Normally, the individual magnetic fields of the body's protons are randomly oriented. During MR imaging, a patient is placed in a static magnetic field, and most of the body's protons will align themselves longitudinally with that field.

Radio frequency pulses are subsequently administered to the patient while in the magnetic field. This will increase the energy state of some of the protons, causing them to displace away from the main direction of the magnetic field, and wobble or rotate at an angle to this field. A radiofrequency

pulse that results in a 90° displacement of protons is typically applied. Cessation of the radio frequency pulse allows the protons to “relax” back into alignment with the original magnetic field. As they relax, they release the previously applied energy as radio waves. These radio waves are picked up at different rates and signal intensities, depending on the tissue type releasing the energy. The waves are picked up by receiver coils in the MRI machine, which convert the energy to electrical signals. The computer uses these electrical signals to form an image.

2. There are two types of relaxation of protons after the radio frequency pulse is stopped. For each type, different tissues have different relaxation times. The variation in relaxation times between different tissues in the body is far greater than the variation in tissue density, so soft-tissue contrast resolution is superior in MR images compared to CT images.

T1 relaxation refers to the return of excited protons to the original energy state of the static magnetic field. Since this represents energy exchange between spinning high-energy protons and the molecular lattice from which they were excited, it is also called *spin-lattice relaxation*.

T2 relaxation describes energy exchange between the magnetic fields of individual protons before and after the application of a radiofrequency pulse. It also includes energy exchanges between protons and local fluctuations in the static magnetic field. T2 relaxation is also called *spin-spin relaxation*.

The time it takes for 63.2% of the protons in a particular tissue to regain the original energy state following the application of a 90° displacing radiofrequency pulse is that tissue's relaxation time (T1 or T2).

3. The time interval between successive applications of radiofrequency pulses during a scan (*repetition time* or *TR*) and the time interval between radiofrequency pulse administration and collection of the resultant radio wave signal by the receiver coils (*echo time* or *TE*) are manipulated in MR imaging. These manipulations are based on known T1 and T2 relaxation properties of tissues.

Imaging a patient using a short (e.g., less than 800 msec) TR and short (e.g., less than 30 msec) TE will lead to hyperintense signals (i.e., white) from tissues with short T1 relaxation times. Tissues with long T1 relaxation times will not have enough time to release much radiofrequency energy between successive excitation pulses (tissue saturation) due to the short TR, and much of what is released will not be received by the coils because of the short TE. This type of imaging is called *T1-weighting*. Water has a very long T1 and T2 relaxation time, whereas fats have short T1 and T2 relaxation times. On a T1-weighted image, water (e.g., CSF, edema) will appear dark, and fat will appear bright. Since there is more fat and less water in white matter versus gray matter, white matter will be brighter than gray matter in a T1-weighted image (Fig. 3.19). With *T2-weighted images*, a long (e.g., more than 2000 msec) TR and a long (e.g., more than 60 msec) TE are used to emphasize tissues with long T2 relaxation times. On a T2-weighted image, water will appear bright

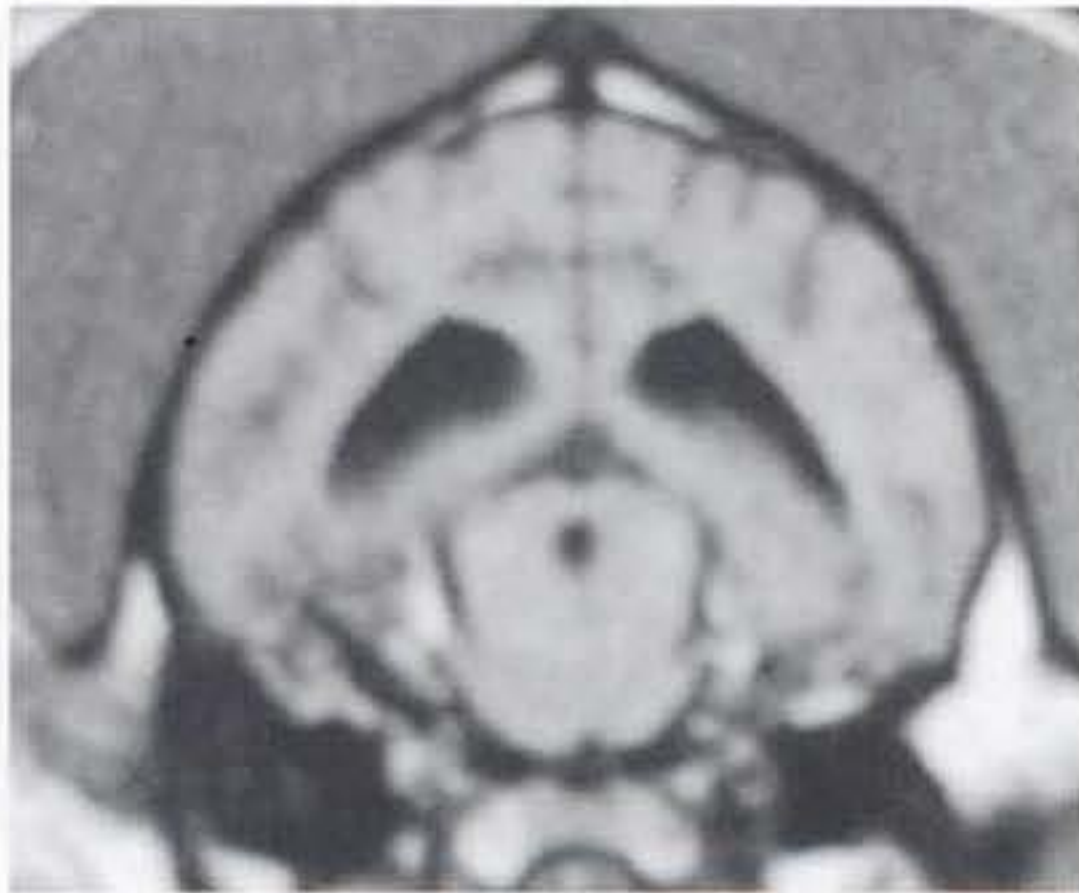


Fig. 3.19. A T1-weighted MR image of a normal dog's brain (transaxial view).



Fig. 3.20. A T2-weighted MR image of a normal dog's brain (transaxial view).

(white), and fat will appear dark or gray. Gray matter will appear brighter than white matter (Fig. 3.20).

Proton-density, or *intermediate weighted*, images are occasionally used to discern fluid-rich solid structures (e.g., edematous tumor, inflammatory foci) from free fluid (e.g., CSF, cysts). These images are obtained using a long TR (e.g., more than 2000 msec) and a short TE (e.g., less than 30 msec). Free fluid will be dark or hypointense, whereas fluid-rich solid structures will be relatively hyperintense (Fig. 3.21).

4. Gadolinium (Gd)-DTPA (diethylenetriaminepentaacetic acid) is a paramagnetic, intravenously administered contrast agent used in MR studies. Similar to meglumine iodine in CT imaging, Gd-DTPA is used to demonstrate abnormalities of the blood-brain barrier (e.g., tumors, inflammatory lesions). Gd-DTPA shortens both T1 and T2 relaxation times of tissues in which it

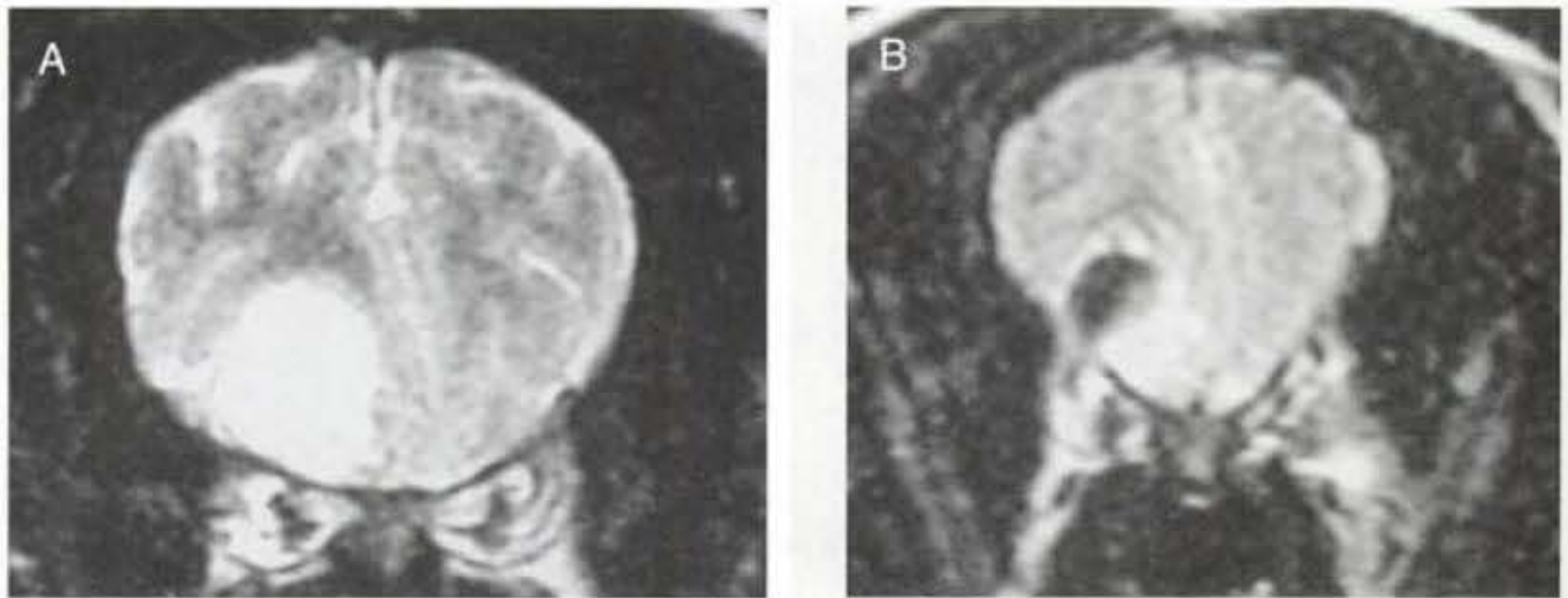


Fig. 3.21. T2-weighted (A) and intermediate-weighted (B) MR images of a cystic cerebral mass (transaxial view) in a dog. Note the sustained brightness of the neoplastic tissue in the intermediate-weighted image, whereas the fluid-containing cyst is bright in the T2-weighted image and dark on the intermediate-weighted image.

localizes, leading to greatest signal intensity on T1-weighted images (Fig. 3.22).

5. Magnetic resonance imaging has been shown to be a very valuable tool in the diagnosis of brain and spinal cord disorders. It is also a very sensitive imaging modality for cauda equina disorders (e.g., degenerative lumbosacral stenosis). For most brain and spine imaging studies, T1-weighted images, T2-weighted images, and T1-weighted images with Gd-DTPA contrast enhancement are obtained.

IV. Electrodiagnostics

Electrodiagnostic examinations take advantage of the body's electrical properties to help characterize neurologic disorders. These tests require both specialized instrumentation and individuals trained in performing the tests. There are numerous electrodiagnostic machines available, the majority of which are capable of performing most or all of the procedures discussed below (Fig. 3.23). There are two main categories of electrical activity measured in clinical neurology: spontaneous and evoked. Spontaneous potentials refers to electrical signals that are produced by the body in the absence of an externally applied stimulus. Evoked potentials are electrical impulses caused by an externally applied stimulus.

A. Spontaneous activity

1. Electromyography (EMG)⁶⁵⁻⁶⁹

- a. Electromyography (EMG) is the recording of spontaneous electrical activity from muscle. This testing is performed with the patient under general

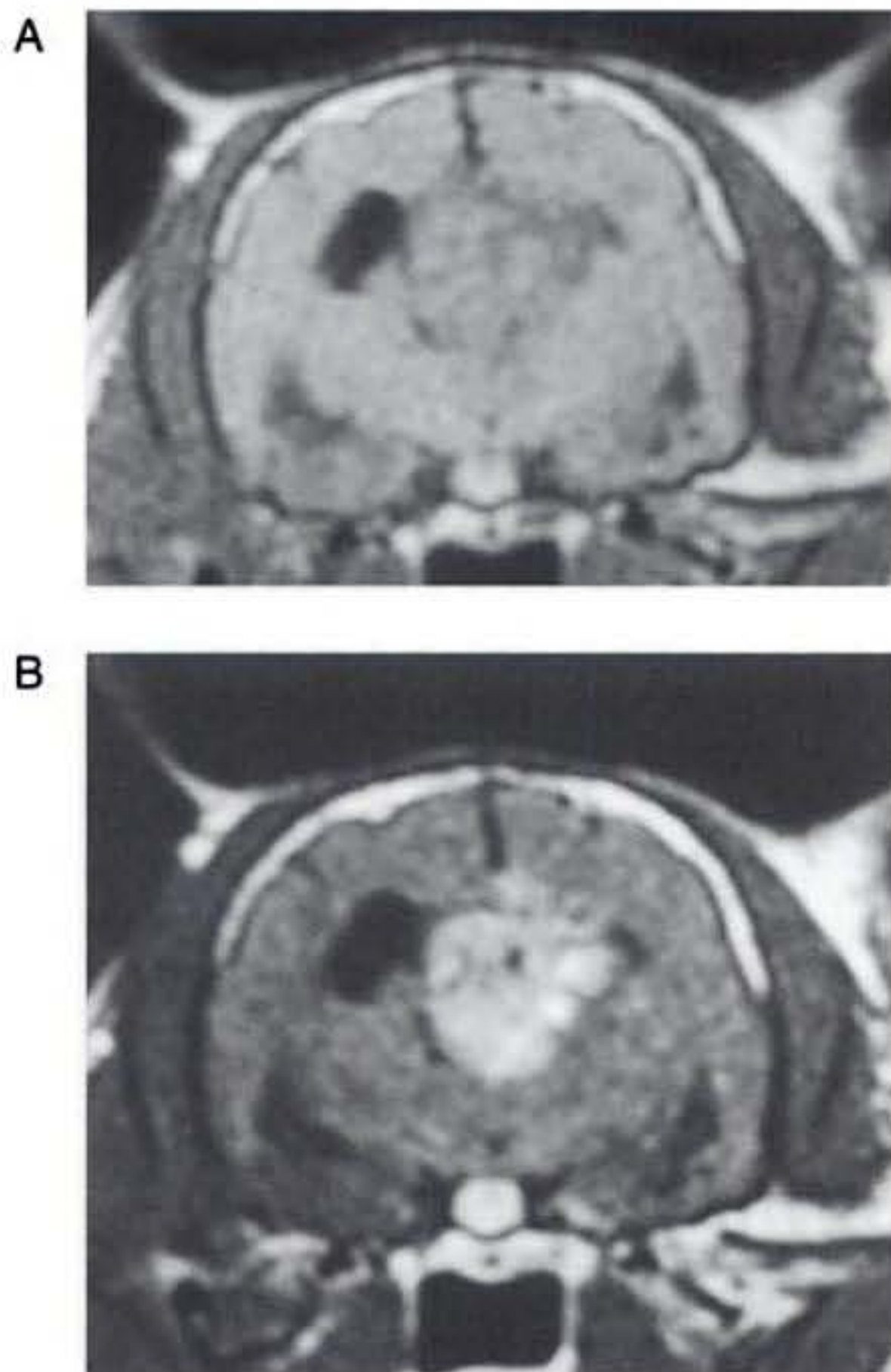


Fig. 3.22. T1-weighted precontrast (A) and postcontrast (B) MR images of an intraventricular mass in a cat's brain with associated hydrocephalus (transaxial view). An ependymoma was suspected.

anesthesia. The authors prefer the use of a concentric needle electrode for EMG studies. The needle electrode is inserted into muscle tissue and muscle activity is recorded. The needle is repositioned several times to sample different areas of the muscle, and multiple muscles are evaluated. Both the sound and appearance of spontaneous muscle activity are evaluated during EMG studies. Abnormal muscle activity from EMG evaluation is sensitive, but not very specific. Muscle fibers often become hyperexcitable with both denervation (due to neuropathies) and more direct damage (myopathies). Therefore, abnormal EMG activity confirms the presence of either a neuropathic or myopathic process, but not specifically one or the other. Electromyographic abnormalities may not be detectable for five to seven days following denervation. It should also be kept in mind that not all myopathies or neuropathies are characterized by abnormal EMG activity.



Fig. 3.23. The Nihon-Kohden Neuropack MEB 2200, a multipurpose electrodiagnostic machine.

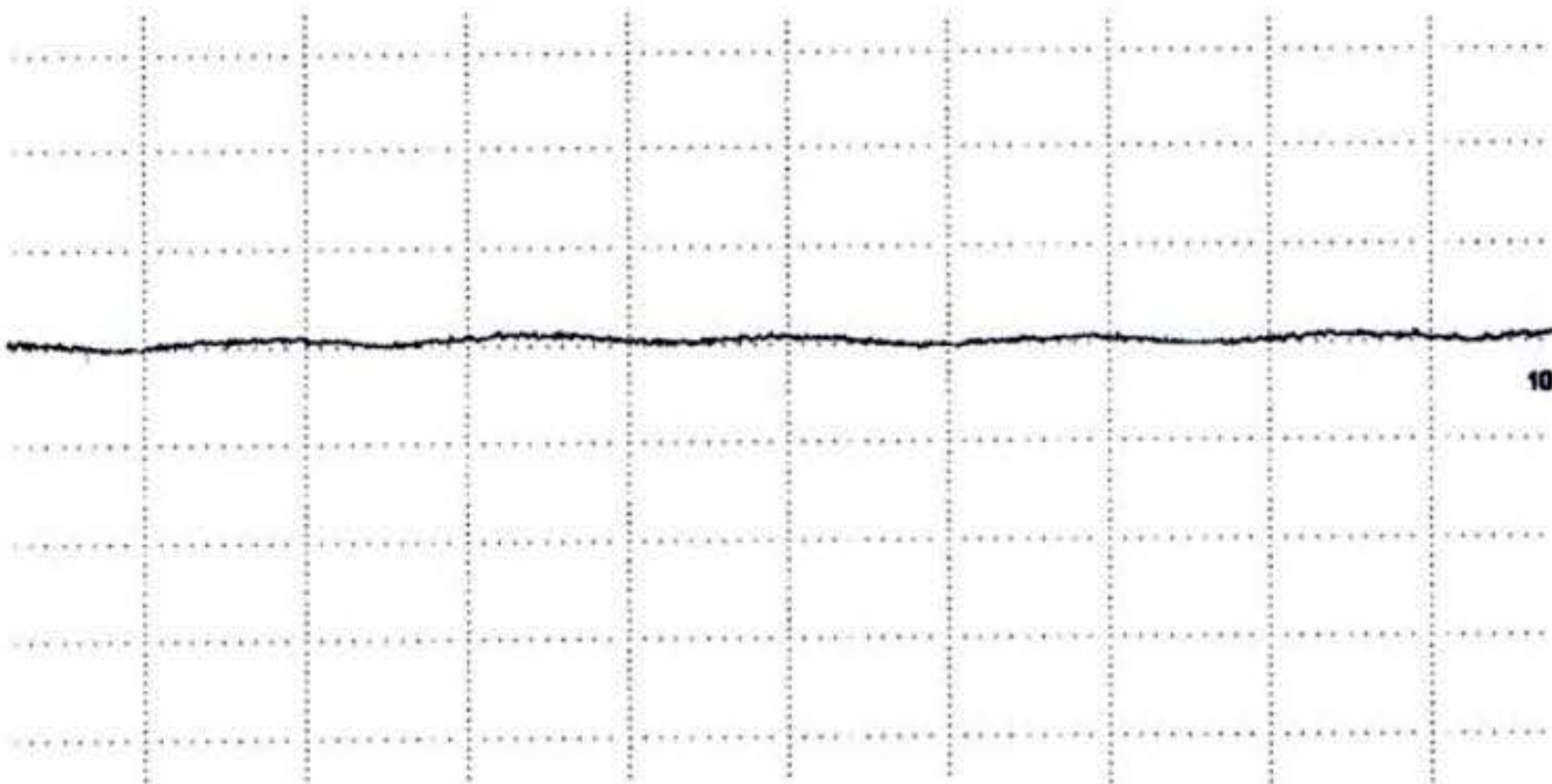


Fig. 3.24. Normal silent EMG tracing from a dog.

- b. In general, muscle tissue is silent on EMG evaluation (Fig. 3.24) of the anesthetized patient. Small deviations from baseline (monophasic potentials) are occasionally recorded from muscles, especially near motor points (sites where major nerve trunks connect with muscle bellies). This normal

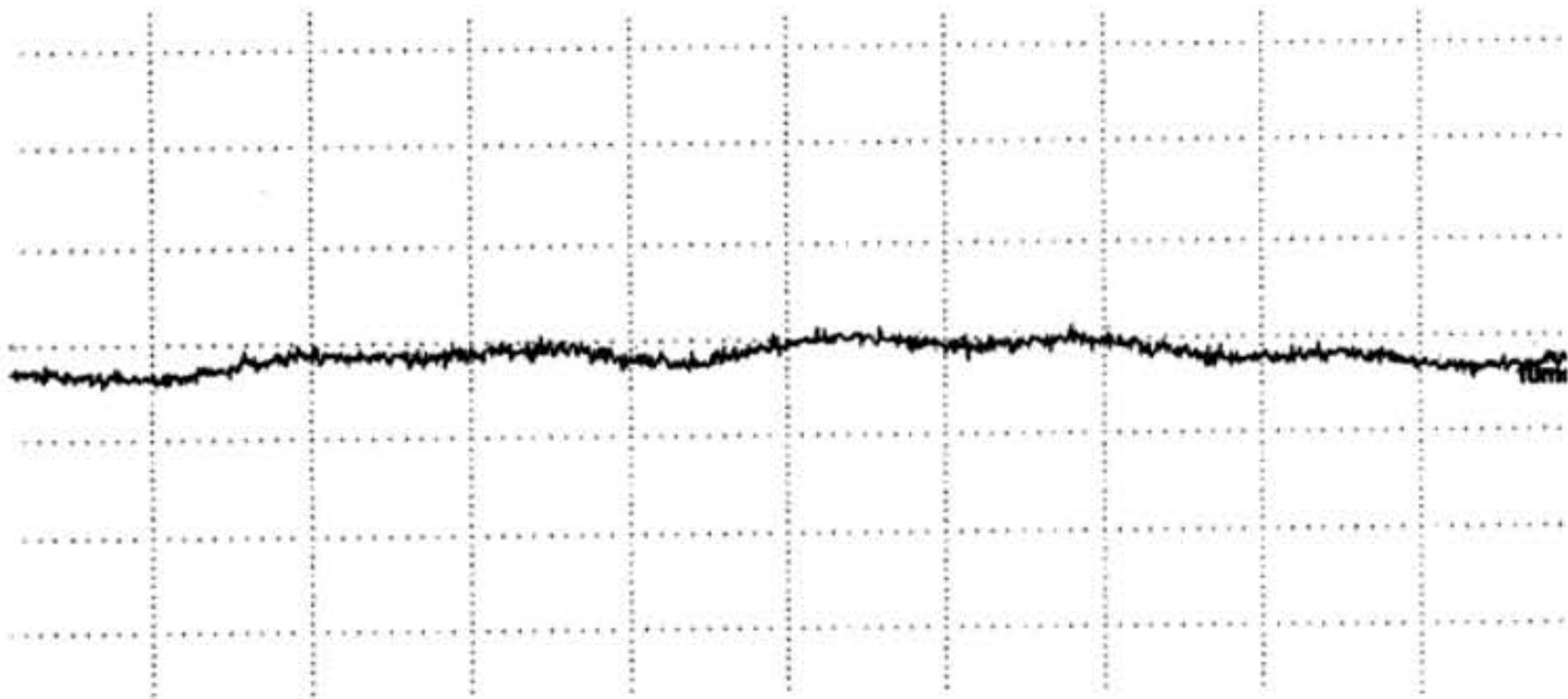


Fig. 3.25. End plate potentials recorded from a normal dog.

activity is called *end plate noise* or *end plate potentials* and reflects small depolarizations (miniature end plate potentials) at neuromuscular junctions (Fig. 3.25). End plate noise sounds similar to small waves breaking at the seashore or the sound heard when one listens to a sea shell. Immediately after insertion of the needle electrode into a muscle belly, there is typically a short burst of electrical activity, called *insertional activity*. This is due to mechanical irritation and damage to muscle fibers by the needle, and is normal unless it lasts more than one to two seconds after the needle stops moving. Replacement of muscle tissue by fat or connective tissue in chronic denervation or myopathies may lead to the absence of insertional activity.

- c. In addition to prolonged insertional activity, abnormal EMG activity includes fibrillation potentials, positive sharp waves, and complex repetitive discharges. In general, all of these abnormal potentials indicate either neuropathy or myopathy, but are not specific for either.

Fibrillation potentials are biphasic or triphasic spikes of short duration that are thought to arise from individual muscle fibers (Fig. 3.26). They sound like popping noises. When occurring as a train or continuous run, the sound is like eggs or bacon frying, or a heavy rain falling on a tin roof. Fibrillation potentials are believed to represent severe or chronic disease, compared with positive sharp waves.

Positive sharp waves often occur concurrently with fibrillation potentials. These potentials are of longer duration than fibrillation potentials and appear to be monophasic (Fig. 3.27). Positive sharp waves are believed to originate from individual muscle fibers, but a conduction block in the sarcolemma leads to the more prolonged potential. When positive sharp waves occur in a train or burst, it sounds like a race car driving past.

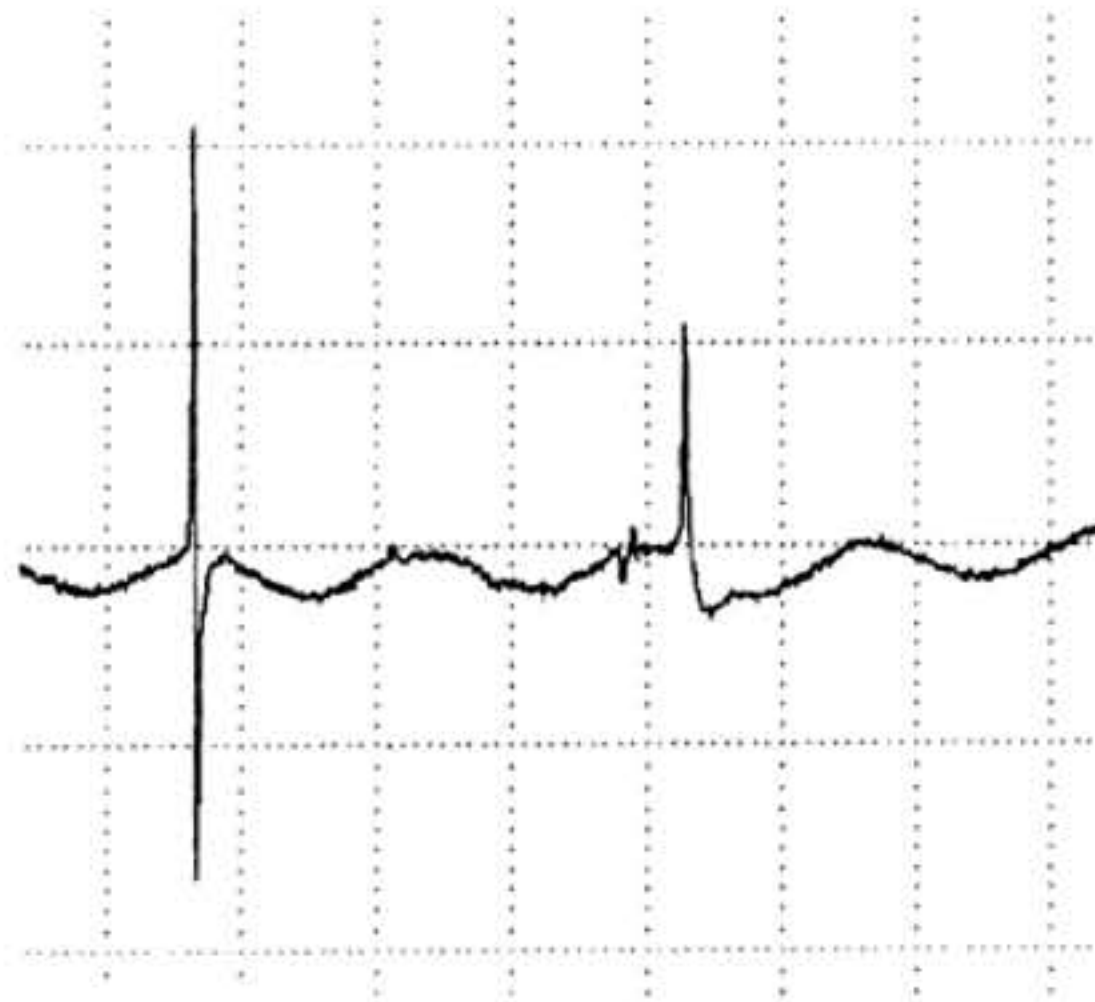


Fig. 3.26. Fibrillation potentials.



Fig. 3.27. Positive sharp waves.

Complex repetitive discharges or bizarre high-frequency potentials are synonymous “catchall” terms applied to polyphasic potentials that do not appear to be fibrillation potentials or positive sharp waves. These potentials are thought to arise from bared muscle spindles and are often associated with chronicity. They tend to have constant amplitude and frequency

(i.e., do not wax and wane). The sounds of these potentials are varied and have been described as revving motorcycle engines, and airplanes flying.

Myotonic discharges are often described as a distinct entity, rather than a subcategory of complex repetitive discharges. These are high-frequency, biphasic or triphasic repetitive discharges that wax and wane, producing a “dive-bomber” sound. They are typically recorded following needle electrode insertion or repositioning. Although not specific for any disorder, these discharges are most often associated with myotonia (either congenital or due to hyperadrenocorticism).

2. Electroencephalography (EEG)^{66,70–72}

- a. Electroencephalography (EEG) refers to the recording of spontaneous electrical activity of the cerebral cortex, and the interpretation of these recordings. Historically, EEG had many practical applications, including its use in localizing seizure foci. In modern veterinary neurology, the clinical utility of EEG examination is limited. The likelihood of EEG examination contributing substantially to the management of a patient with an established generalized seizure disorder is low. As a localizer of focal brain abnormalities, EEG is fairly inaccurate and provides no structural information. The increased availability and use of CT and MR technology has been associated with a decrease in the use of EEG examinations. However, EEG remains an important diagnostic tool.

Electroencephalography is often helpful in cases of focal seizure disorders, in which the diagnosis of the condition as a seizure disorder is sometimes equivocal. The authors have also found EEG examination useful as a determinant of brain death in comatose patients who have been resuscitated following cardiac arrest. When EEG examination is performed in this latter context, it is usually done so in conjunction with a BAER examination.

- b. Electroencephalography is performed using small scalp recording electrodes. These electrodes are placed in specific areas so that electrical activity in multiple regions of the cerebral cortex can be simultaneously recorded (Fig. 3.28). Each channel (derivation) represented on the EEG recording represents electrical potentials occurring between two scalp electrodes, the first of the named pair being the exploring electrode, the second being the reference electrode. The arrangement of multiple derivations of electrode pairs is referred to as a montage.

There are multiple ways to perform an EEG examination. Since abnormal EEG activity is likely to occur during physiologic sleep, and since general anesthesia may induce spike activity (associated with seizure disorders) in normal patients, it is not recommended to perform EEGs in anesthetized patients. The authors prefer to perform EEGs in a quiet darkened room with the patient lightly sedated (e.g., meperidine, 5 mg/kg intramuscularly). The patient typically will become drowsy and fall asleep,



Fig. 3.28. Typical scalp electrode arrangement for EEG recording.

allowing the measurement of both awake and sleeping EEG activity. A full EEG recording takes approximately 20–40 min to perform.

- c. Normal background electrical activity recorded on EEG examination primarily reflects the algebraic summation of oscillating resting membrane potentials and subthreshold postsynaptic potentials (PSPs) of cerebral cortical neurons (Fig. 3.29). Electrical activity of cerebral cortical neurons is influenced by the ascending reticular activating system (ARAS) of the brain stem, primarily the diencephalon. Fluctuations in membrane potentials of glial cells in the cerebrum probably also contribute to the EEG pattern. In general, the alert state is characterized with high-frequency, low-voltage activity. The frequency slows and the amplitude of measured potentials increases with drowsiness and non-REM (rapid eye movement) sleep. The EEG pattern of REM sleep is similar to the awake EEG pattern.

There is often a high degree of subjectivity in the interpretation of abnormal EEG recordings. In general, frequencies and amplitudes that appear either inadequate or excessive for the physiologic conditions under which they are measured (e.g., high-voltage, slow frequency activity in an awake patient) are indicative of brain dysfunction. Spike and spike-wave activity (Fig. 3.30) are indications of a seizure disorder.

B. Evoked activity

1. Brain-stem auditory evoked response (BAER) test^{25,66,67,73–76}

- a. Brain-stem auditory evoked response (BAER) testing utilizes the auditory pathway for the evaluation of hearing and brain-stem disorders. The patient is administered auditory stimuli in the form of clicks delivered via specialized ear plugs. The resultant evoked response is measured via subcutaneous scalp electrodes arranged in specific patterns. The normal BAER consists of four or five waves that are time-locked to the sound

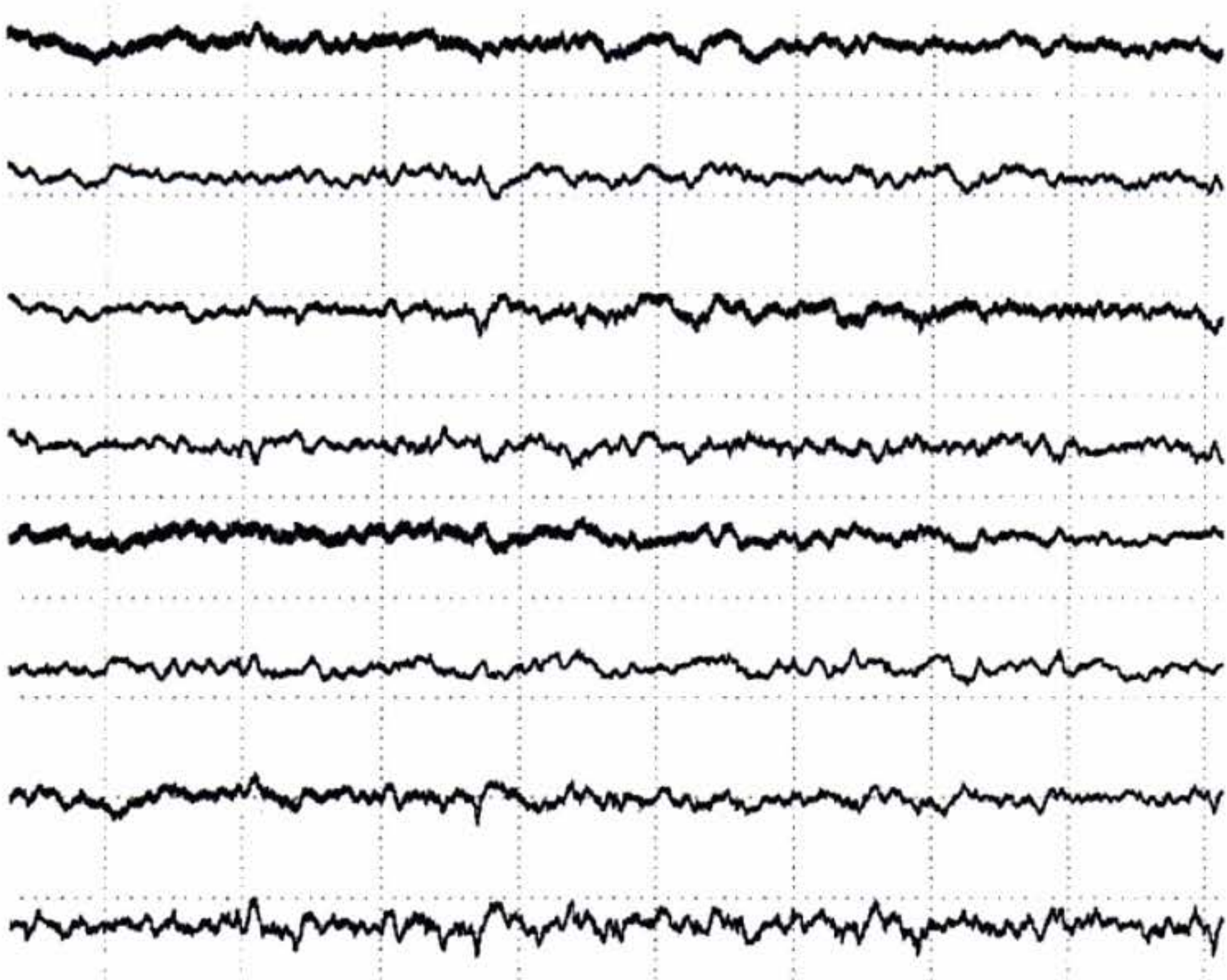


Fig. 3.29. Normal EEG recording from a dog.

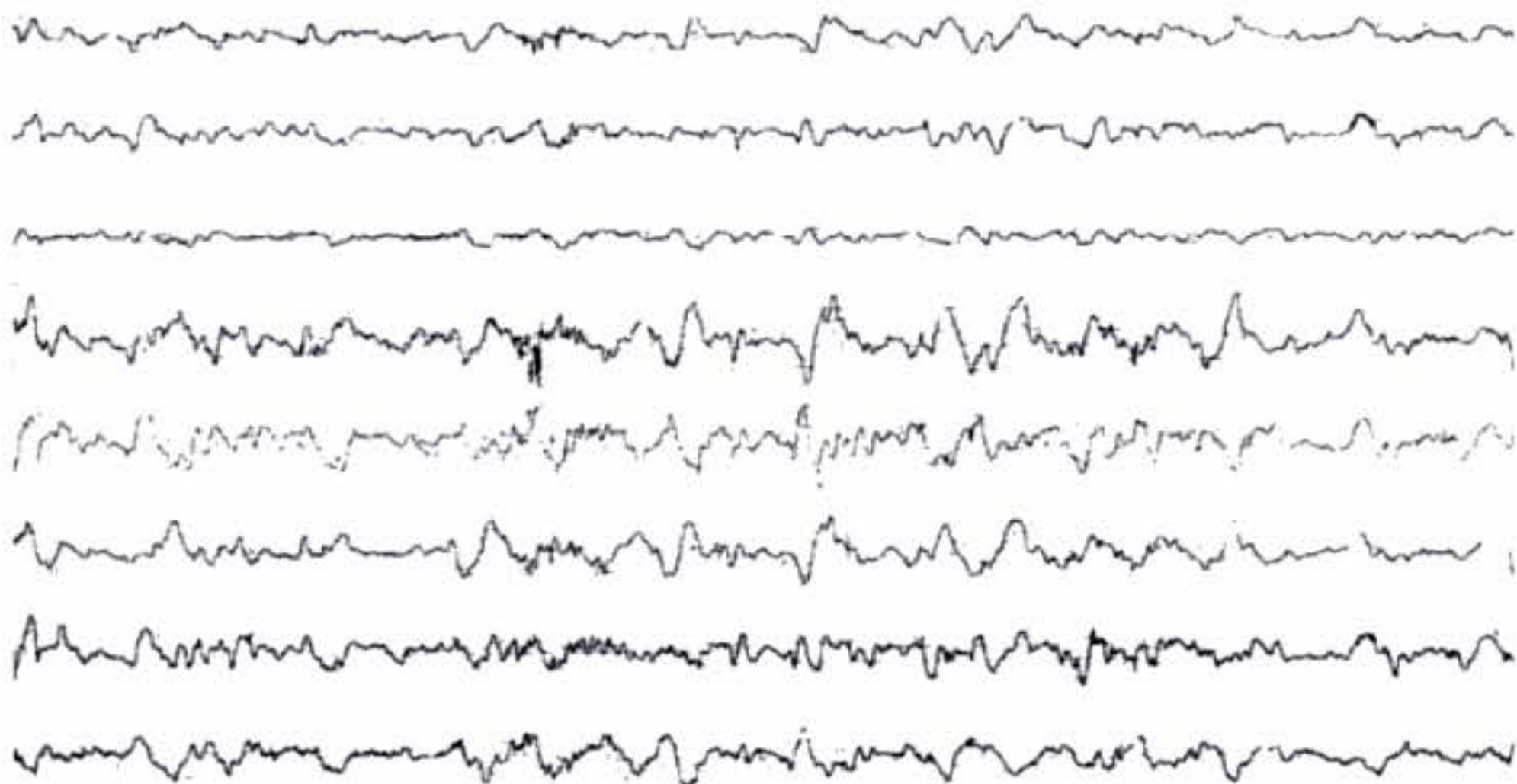


Fig. 3.30. Spike activity from an EEG recording of a patient with seizure activity (Courtesy of Dr. Gregg Kortz).

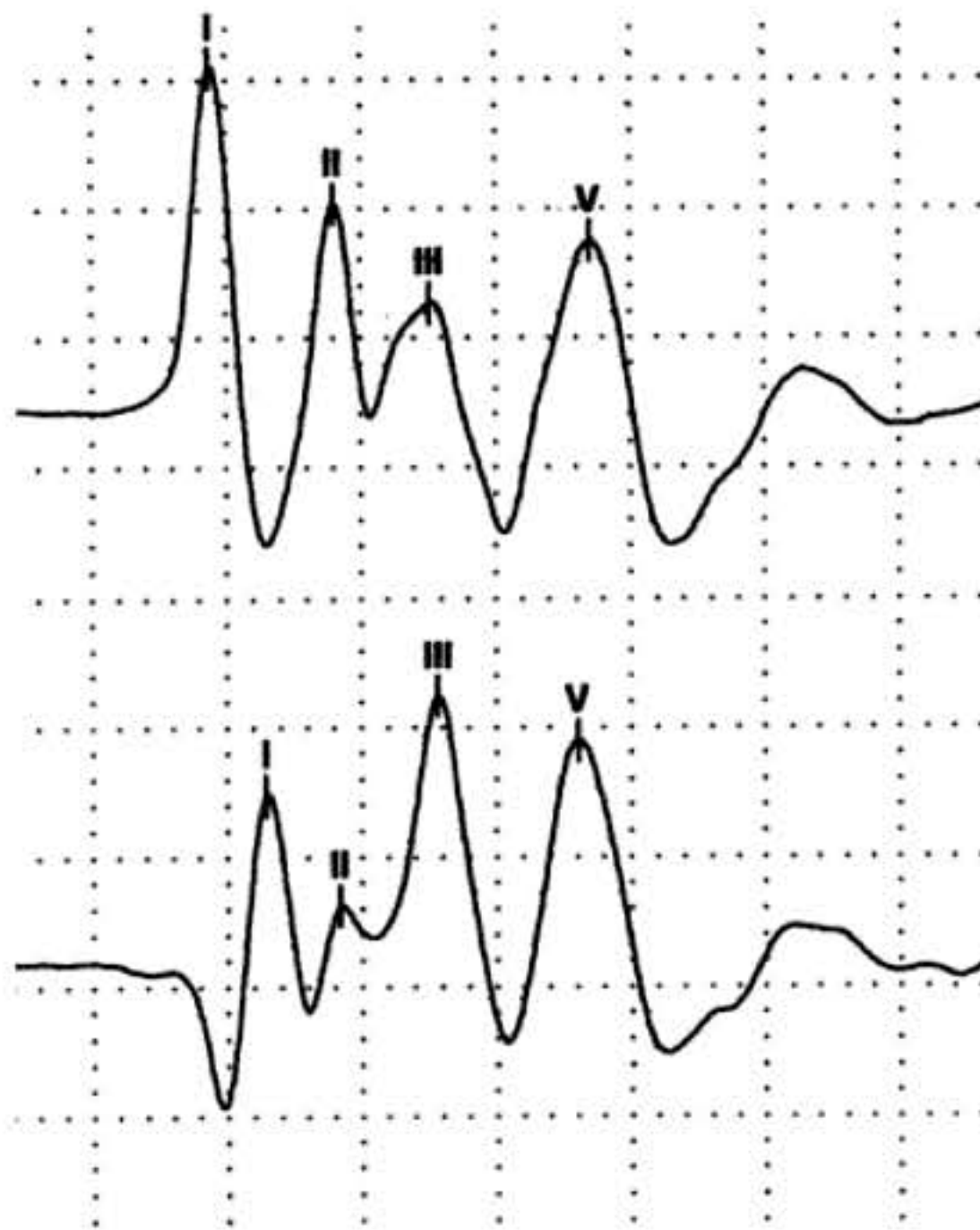


Fig. 3.31. Normal BAER recording from a cat.

stimulus. These waves appear within 10 ms of the sound delivery (Fig. 3.31). The BAER is not appreciably affected by sedation or anesthesia, so it can be performed on awake, sedated, or anesthetized patients.

- b. The waves of the BAER correspond to sequentially activated neuronal groups and white matter tracts associated with the auditory pathway. These waves represent a caudal to rostral chain of propagated depolarization. The appearance and latency (time between the sound stimulus and appearance of the wave) of each wave following the first wave is dependent upon the integrity of neural tissue caudal to the specific wave's site of generation, as well as upon the tissue comprising the generator site for that specific wave.

There is general agreement that wave I is generated by the cochlear portion of the vestibulocochlear nerve. The generator sites of the remaining waves are not definitively known, and probably represent superimposition of action potentials from multiple brain-stem structures. Wave II is thought to arise from the cochlear nuclei in the medulla. Wave III is suspected to be generated by the rostral olivary nuclei and the dorsal nuclei of the trapezoid body, both located in the medulla. Wave IV likely represents action potentials from the lateral lemniscus and lemniscal nuclei of the pons. The caudal colliculi of the midbrain and medial geniculate nuclei of the diencephalon contribute to the generation of wave V.

- c. When performing the BAER, the patient is placed in ventral recumbency, the scalp electrodes are attached, and the ear plugs are inserted. Each ear is stimulated separately, typically at 80 and 100 decibels (dB). The nonstimulated ear receives a masking or “white” noise 30–40 dB below that of the stimulated side. Similar to an electrocardiogram or an EEG, the BAER can be recorded with different arrangements of recording electrodes. The authors prefer a vertex to mastoid recording (VM), and occasionally record additionally with a vertex to first thoracic vertebra (VT1) lead arrangement. These two types of recording can be accomplished concurrently. Wave IV is often indistinguishable as a separate wave on the VM recording, and may be complexed with either wave III or V.
 - d. The appearance of four or five recognizable waves on a BAER recording confirms hearing ability on that side. A flat line is evidence of deafness (Fig. 3.32). Dogs with congenital sensorineural deafness (see Chapter 7) typically have flat BAER recordings at both 80 and 100 dB either unilaterally or bilaterally. A flat line, or relatively decreased amplitude of waves at 80 dB, and a detectable response at 100 dB suggest a conduction disturbance of hearing (e.g., fluid in the middle ear cavity due to otitis media). Similarly, a prolonged latency from sound stimulus to the appearance of wave I at 80 dB that improves at 100 dB suggests a conduction disturbance of hearing. For evaluation of brain-stem integrity, interwave intervals are calculated by the computer for peak to peak latencies between waves I and III, waves III and V, and waves I and V. These intervals should be within reference ranges and should also not differ from right to left by more than 0.1 ms. Brain-stem lesions (e.g., tumors) will cause a conduction delay, which will be measured as a prolonged latency that corresponds to the anatomic location of the lesion (Fig. 3.33). Although wave amplitudes are not often calculated for diagnostic purposes, a V/I amplitude of less than 0.5 is indicative of a brain-stem lesion. A patient that has experienced brain death will typically exhibit a flat BAER, or have only wave I present on the recording.
2. Motor nerve conduction velocity (MNCV)^{66–68,77–79}

Motor nerve conduction velocity (MNCV) studies are performed primarily in animals suspected of having neuropathies. For MNCV measurement, an

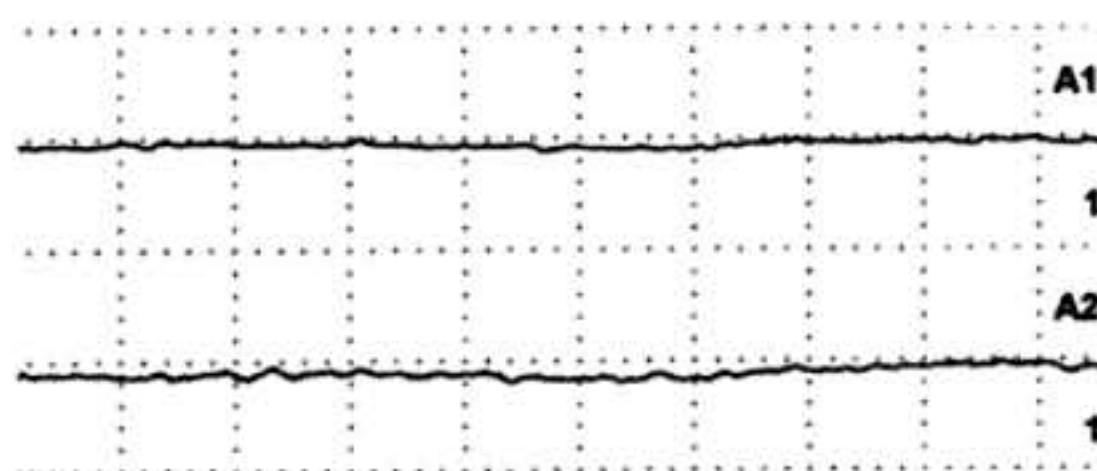


Fig. 3.32. Flat line BAER recording from a puppy with congenital sensorineural deafness.

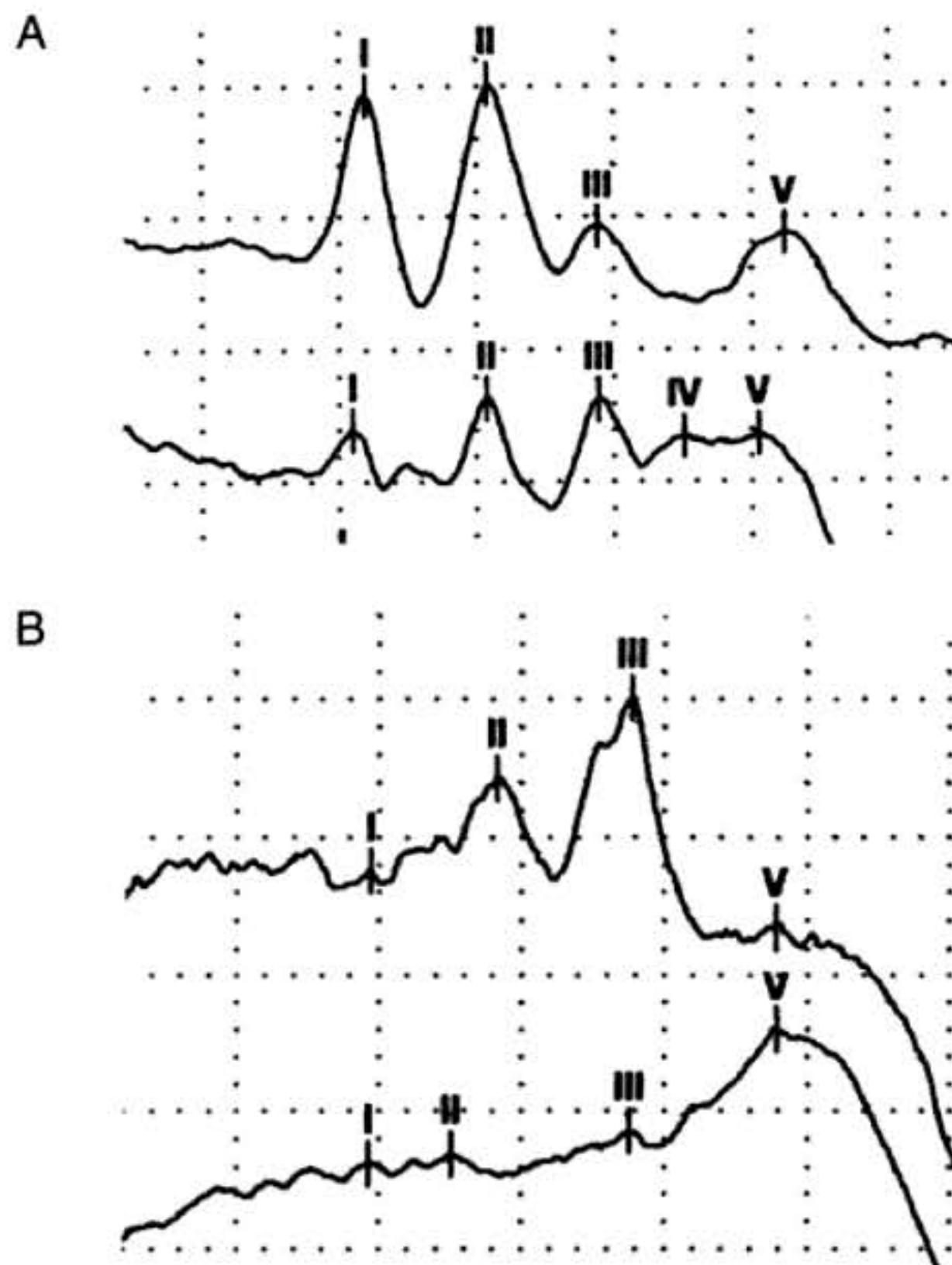


Fig. 3.33. BAER recordings from a dog with a brain-stem lesion, after stimulating the left (A) and right (B) ears. Note the lack of symmetry between sides and the prolonged interwave latency on the second recording.

electrical stimulus is applied to a nerve with subcutaneous electrodes, and the resultant depolarization of a muscle supplied by that nerve is recorded with a recording electrode. The depolarizing event is a large biphasic or triphasic muscle potential formed by action potentials of many muscle fibers from many motor units. It is usually referred to as a compound muscle action potential (CMAP) or an M wave. The latency, or time, from the stimulus to the onset of the M wave is measured by the computer. A minimum of two sites of a nerve must be stimulated in order to calculate a MNCV. The distance between the two stimulation sites (in meters) is divided by the difference in latency from stimulus artifact to M wave appearance for the two sites (in seconds) to arrive at MNCV in m/sec. The M wave is the result of orthodromic (proximal to distal) propagation of nerve depolarization.

When a nerve is artificially stimulated as in MNCV testing, it also depolarizes antidromically (distal to proximal). Recording conditions can be set to measure one of two smaller waves—F waves or H waves. F waves result from antidromic motor nerve depolarization causing depolarization of lower motor

neurons in the ventral horn of the spinal cord. This depolarization leads to a secondary orthodromic nerve depolarization back down the axon. The subsequent muscle response (F wave) is of much smaller amplitude and longer latency than the M wave. Similarly, the H wave is due to initial antidromic, then orthodromic propagation of depolarizing events. However, the H wave represents an electrically elicited stretch reflex. Rather than directly causing motor neuron depolarization from an antidromic volley up the motor axons, the H reflex involves antidromic depolarization that follows the sensory axons (e.g., Ia axons) into the spinal cord gray matter, leading to motor neuron depolarization. This motor neuron depolarization leads to a secondary muscle depolarization (H wave) of smaller amplitude and greater latency than the M wave. A smaller stimulus intensity than that used for F wave recording is necessary for H wave measurement. F and H waves are used primarily to evaluate diseases with nerve root pathology (e.g., polyradiculoneuritis).

General anesthesia is required for MNCV measurement. If the patient has clinical evidence of a generalized disorder (e.g., suspect polyneuropathy), the authors prefer using the sciatic nerve and its branches (i.e., peroneal or tibial nerves). After a nerve is severed, axons distal to the severed area will continue to conduct normally for up to four days. The nerve is stimulated at two or three sites and the MNCV is calculated after manually measuring the distance from stimulating to recording electrodes (Fig. 3.34). This measurement is performed using a tape measure and is the most likely source of error in this test. Normal MNCV is at least 50 m/sec in older patients, and is typically greater than 60 m/sec in young to middle-aged animals. Decreased body temperature may affect MNCV. The MNCV decreases by 1.8 m/sec for each drop in degrees celsius from normal. Proximal nerve segments have faster MNCVs than distal nerve segments. In general, demyelination is more likely to cause slowed MNCV than is axonal loss. Small amplitude M waves or polyphasic M waves are often indicative of neuropathy but may result from myopathies also.

3. Sensory nerve conduction velocity (SNCV) and somatosensory evoked potentials (SSEP)^{66-69,80-84}

Sensory nerve conduction velocity (SNCV) is typically measured in dogs and cats by stimulating a distal cutaneous nerve branch, and measuring compound action potentials (CAPs) over proximal sites on the parent nerve. The technique is similar to that used for MNCV, but the depolarization events of interest are antidromic and CAPs from axonal depolarization are of much smaller magnitude than the CMAPs or M waves recorded in MNCV studies. Sensory nerve conduction velocity recording is primarily used to evaluate patients with suspected neuropathies, especially if MNCV evaluation is normal or equivocal. It is generally thought that SNCV is more sensitive an indicator of early neuropathic processes, compared to MNCV.

By placing needle recording electrodes near the interarcuate space over selected regions of the spinal cord, and/or over the scalp region, evoked activity of the central nervous system can be recorded following stimulation of a

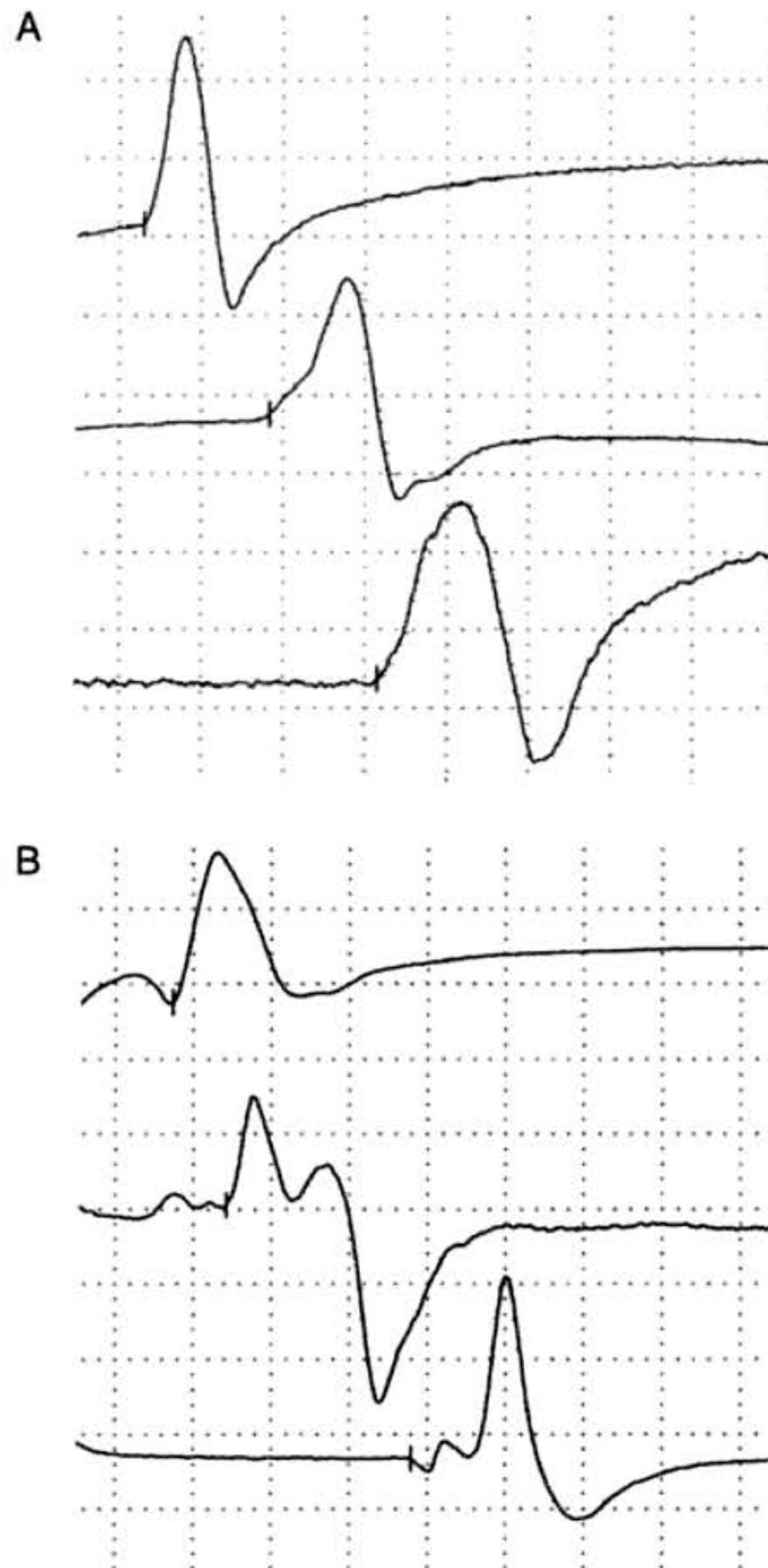


Fig. 3.34. MNCV recordings (M waves) from the sciatic and peroneal nerves of a normal dog (A) and a dog with a progressive polyneuropathy (B). Polyphasic M waves are apparent on the second recording.

peripheral sensory nerve. This latter type of electrodiagnostic testing is referred to as somatosensory evoked potentials (SSEP). Depolarizing events recorded on an SSEP recording are due to axonal CAPs in the cauda equina region or spinal cord white matter (similar to the CAPs of peripheral nerves)

as well as from gray matter field potentials. Field potentials refer to depolarization/repolarization events occurring in a group of neurons (e.g., interneuron pool) following excitation from an incoming volley of action potentials (i.e., from peripheral stimulation). Recording over the cervical and lumbosacral intumescence areas often results in a high-amplitude, long-duration potential, primarily due to these depolarization/repolarization events. These potentials are referred to as *cord dorsum potentials*. SSEP studies are used primarily to evaluate the functional integrity of the spinal cord ascending pathways.

The setup for SNCV and SSEP is similar. These studies are also performed under general anesthesia. The authors prefer to stimulate the distal branches of the peroneal nerve and record over proximal segments of the peroneal and sciatic. Recording is usually accomplished by leaving the stimulating electrodes from the MNCV in place, and converting these to recording electrodes. Additional recording electrodes can be placed along the spine or scalp, and SSEP recordings can be made simultaneously with SNCV recordings (Fig. 3.35).

4. Repetitive nerve stimulation (RNS)^{67,68,85-87}

The repetitive nerve stimulation (RNS) test measures successive CMAPs (M waves) induced by repetitively stimulating the nerve that supplies the muscle from which the potentials are recorded. With stimulation rates of five per second or less, the sequential M waves should be of equal amplitude and area as the first. A decremental response of 10% or greater indicates a problem with neuromuscular transmission. Though not specific for the disease, a decrementing RNS is usually indicative of myasthenia gravis (Fig. 3.36).

General anesthesia is required for RNS in dogs and cats. The authors prefer stimulating the peroneal nerve at the knee or hock level, and recording from a digital muscle. The setup is the same as for MNCV, but only one stimulation site is necessary for RNS. In cases of focal MG, the limb RNS is sometimes normal. In suspect cases of focal MG with normal limb RNS, the authors have often demonstrated a decremental response in facial musculature (e.g., orbicularis oculi muscle) following facial nerve stimulation.

5. Miscellaneous evoked response tests^{67,86,87-91}

The use of magnetic motor evoked potentials (MEPs) to evaluate descending motor pathways has been described in dogs. A magnetic field is applied to the cranium to stimulate regions of the cerebral motor cortex, and recordings of CMAPs (M waves) are made from limb muscles. Recordings of depolarizing events can also be obtained from the spinal cord and peripheral nerves. Magnetic MEPs can be recorded under sedation.

Single-fiber electromyography (SF-EMG) has also been described in dogs. This procedure makes use of a specialized needle electrode that records evoked action potentials from individual muscle fibers. The variability of neuromuscular transmission time for individual muscle fibers, referred to as "jitter," is recorded. This test is both sensitive and specific for acquired MG in people (increased "jitter"), and may hold promise as a diagnostic test for that

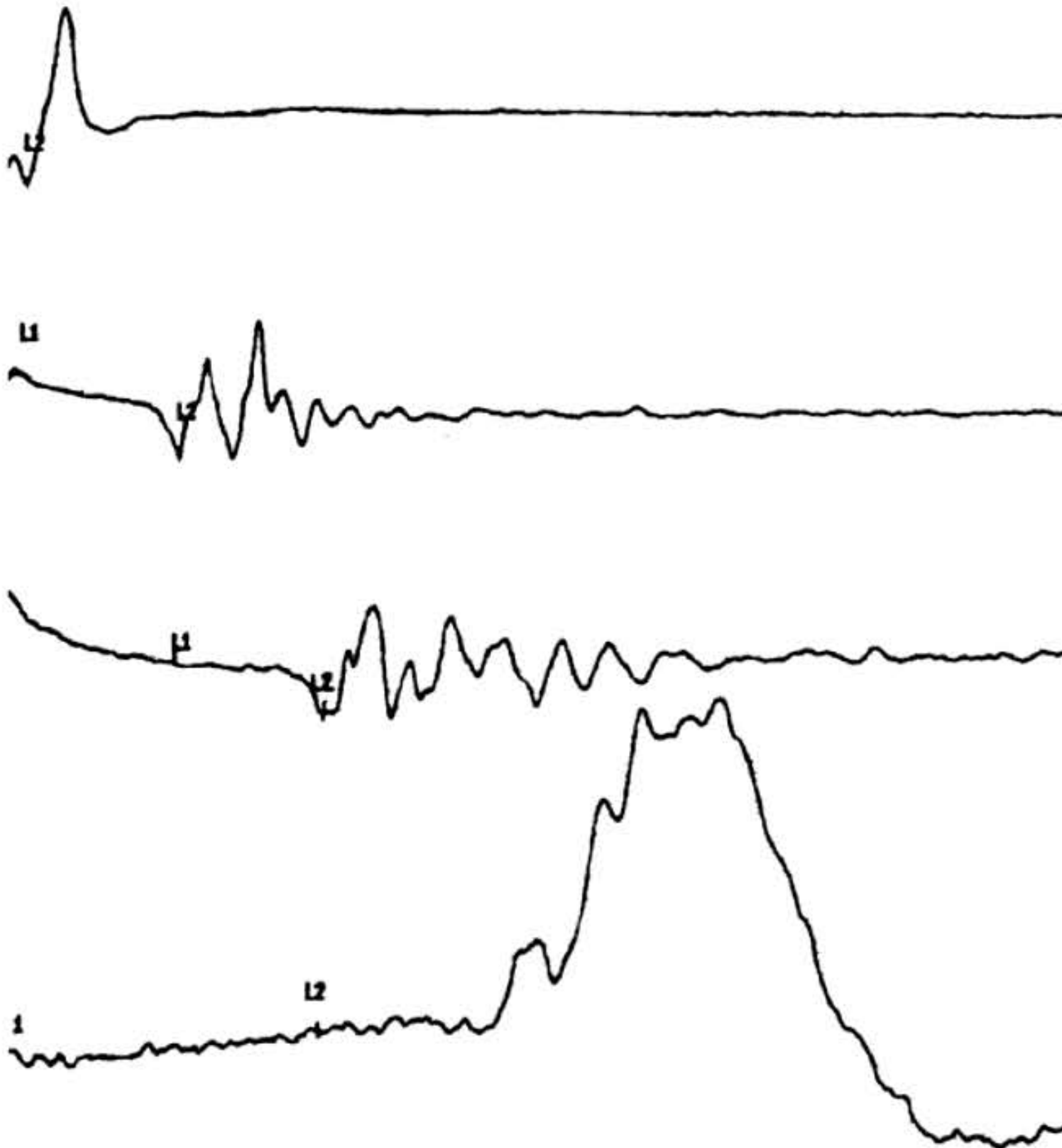


Fig. 3.35. Simultaneous SNCV (top three waves represent peroneal/sciatic nerve at hock, stifle, and hip regions) and SSEP (bottom recording represents the lumbosacral intumescence) recordings following distal peroneal nerve stimulation in a dog (Courtesy of Dr. Gregg Kortz).

disease in dogs. Single-fiber EMG can also be performed under sedation, versus general anesthesia.

V. Biopsy/exploratory surgery^{25,92,93}

- A. Nerve and muscle biopsies are often performed in conjunction with electrodiagnostics. These should be used to help characterize and diagnose neuropathies and myopathies.
- B. Exploratory spinal surgery is performed when imaging techniques do not adequately characterize a compressive spinal cord lesion, or when biopsy and debulking or resection of a neoplastic lesion is indicated.

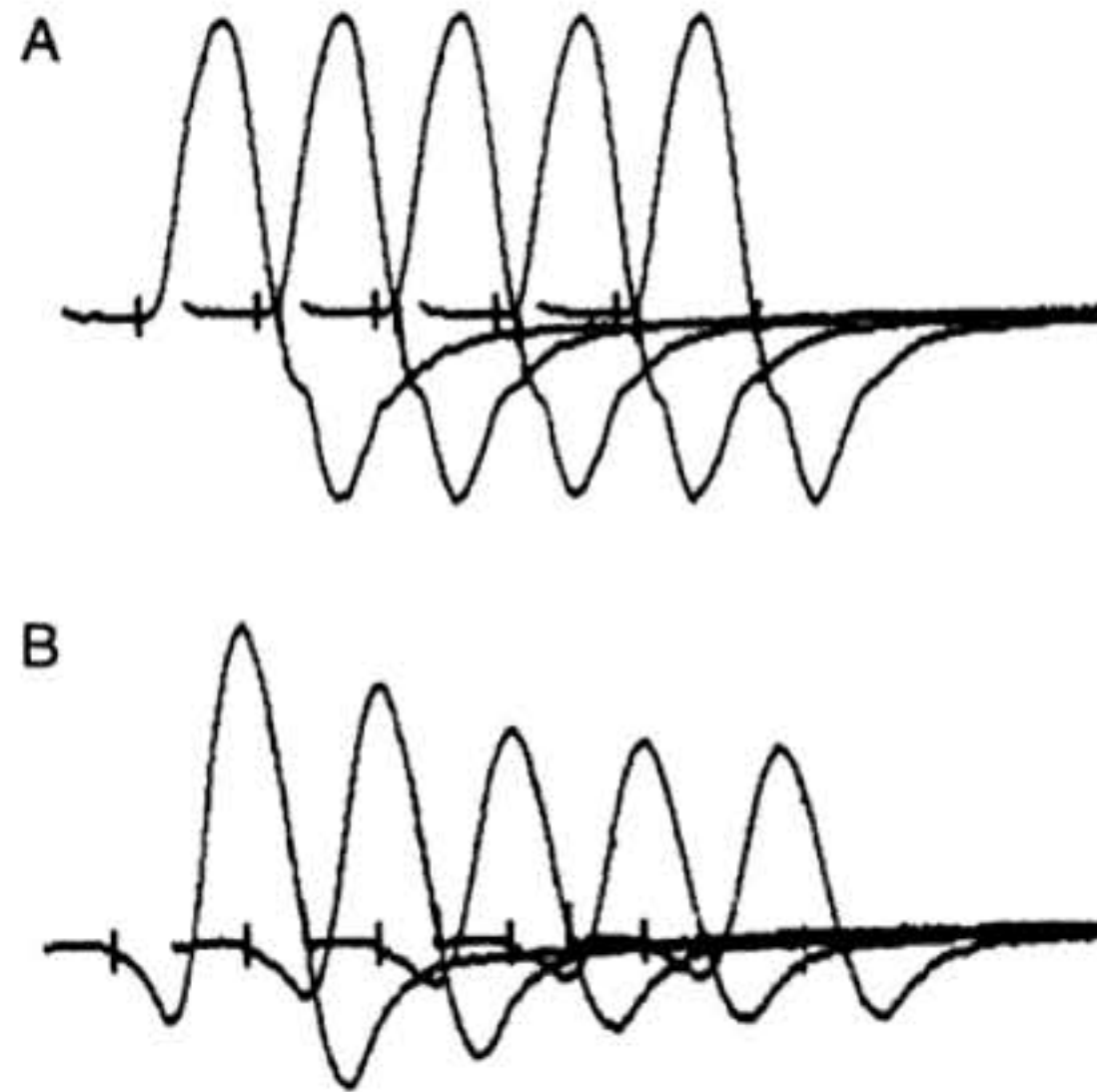


Fig. 3.36. Normal RNS result (A) compared to a decrementing RNS recording (B). The latter recording is from a myasthenic dog (Reprinted with permission⁸⁷).

C. Exploratory craniotomy is indicated for biopsy and debulking of neoplastic lesions seen on CT or MRI. Stereotactic brain biopsy is becoming more widely available for diagnosis of intracranial lesions without exploratory surgery.

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Chapter 4

ENCEPHALOPATHIES: DISORDERS OF THE BRAIN

Curtis W. Dewey

I. Introduction

This chapter focuses on brain diseases other than head trauma and cerebellar disorders. These latter subjects are discussed in detail in Chapters 5 and 8, respectively. There are a large number of diseases that can affect the brain, the majority of which are discussed in this chapter. Seizures will be mentioned where appropriate, but the important subject of seizure disorders and their management is discussed in detail in Chapter 6. Many of the disease processes that affect the brain can cause dramatic clinical signs, which can be very upsetting to the owner and even the clinician. However, many of these diseases can be successfully treated. The clinician should be cautious not to rush into making prognostic decisions based primarily on clinical appearance.

II. Clinical Signs of Brain Dysfunction (see also Chapter 1)

A. Cerebrum/diencephalon (forebrain)

Dogs and cats with forebrain dysfunction may exhibit clinical signs that include altered mental status (obtundation more likely than stupor or coma), behavioral changes, circling in a wide arc, head-pressing, visual impairment, focal and/or generalized seizure activity, and hemi-inattention (unilateral hemineglect) syndrome. Conscious proprioceptive deficits with a normal to near-normal gait is characteristic of forebrain dysfunction. Neck pain may be appreciable in patients with structural forebrain lesions.

B. Brain stem (caudal to the diencephalon)

Lesions from the midbrain (mesencephalon) through the medulla (myelencephalon) may lead to altered mental status (stupor or coma more likely than with forebrain lesions), proprioceptive and gait abnormalities, deficits in cranial nerves III–XII, and central vestibular dysfunction.

III. Disorders Affecting the Brain in Dogs and Cats (see Table 4.1)

A. Degenerative

1. Lysosomal storage disease^{1–17}

- a. This disease category comprises a wide variety of inherited (most are autosomal recessive) abnormalities, which have in common the intracellular accumulation of one or more products of an interrupted degradative metabolic pathway. In the normal animal, substances that need to be

Table 4.1: Encephalopathies of Dogs and Cats

Degenerative	Anomalous/ Developmental	Metabolic	Neoplastic	Nutritional	Inflammatory/ Infectious	Ischemic/ Vascular
Lysosomal storage disease	Congenital hydrocephalus	Hepatic encephalopathy	Primary brain tumors	Thiamine deficiency	Bacterial meningoencephalitis	Global ischemia Thromboembolic disease
Leukodystrophy/ spongy degeneration	Dandy-Walker syndrome	Renal-associated encephalopathy	Secondary brain tumors		Fungal meningoencephalitis	
Neuronal vacuolation of Rottweilers	Intracranial intra- arachnoid cyst	Hypoglycemic encephalopathy			Viral meningoencephalitis	
Multisystem neuronal degeneration/ abiotrophy of Cocker spaniels	Neuronal migration disorders	Electrolyte- associated encephalopathy			Protozoal meningoencephalitis	
	Miscellaneous malformations	Miscellaneous endocrine-related encephalopathies			Rickettsial meningoencephalitis	
Cognitive dysfunction syndrome		Acid-base disturbance encephalopathy			Verminous meningoencephalitis	
		Mitochondrial encephalopathy			Miscellaneous infectious meningoencephalitis	
					Granulomatous meningoencephalitis (GME)	
					Necrotizing meningoencephalitis of small-breed dogs	
					Eosinophilic meningoencephalitis	
					Hydrocephalus with periventricular encephalitis	

catabolized within the cell typically undergo a stepwise degradation by a sequential chain of specific lysosomal enzymes. If an enzyme (acid hydrolase) in the chain of degradation is absent or defective (e.g., deficiency of an activator protein for that enzyme, deficiency of a lysosomal transport protein for the substance to be degraded), the substance prior to that enzymatic step accumulates. The accumulated by-product(s) leads to cellular dysfunction, presumably due to cellular swelling, a toxic effect of the accumulated material(s), or both. These materials include sphingolipids, glycosaminoglycans, glycolipids, glycoproteins, and oligosaccharides. Because neurons of the central nervous system are a permanent, nondividing cell population, many of the lysosomal storage diseases result in clinical signs of neurologic dysfunction at an early age.

There is a multitude of lysosomal storage disorders reported in a variety of dog and cat breeds. Globoid cell leukodystrophy (Krabbe's disease) is due to a deficiency of galactosylceramidase I, which leads to the accumulation of a sphingolipid (psychosine). Psychosine is toxic to oligodendrocytes and Schwann cells, so white matter in both the central and peripheral nervous system is affected. Globoid cell leukodystrophy (GCL) has been reported most commonly in West Highland White and Cairn terriers. Other dog breeds reported with GCL include Pomeranian, miniature Poodle, Bassett hound, Beagle, and Blue Tick hound. Domestic shorthaired cats have also been reported with GCL. The gangliosidoses—gangliosidosis I (GMI) and gangliosidosis II (GMII)—are due to deficiencies of beta-galactosidase and beta-hexosaminidase (A, B, or both), respectively. Gangliosidosis I (Norman-Landing disease) has been reported in Siamese and domestic shorthaired cats as well as in several dog breeds, including English Springer spaniel, Portugese water dog, and Beagle crossbreeds. Gangliosidosis II (Derry's disease) has been described in the German shorthaired pointer and Japanese spaniel, in addition to Korat, Siamese, and domestic shorthaired cats. Gaucher's disease is due to a glucocerebrosidase deficiency and has been reported in Australian Silky terrier dogs. Niemann-Pick disease (sphingomyelinase deficiency, or a cholesterol transport defect) has been primarily reported in cats (Siamese, Balinese, domestic shorthaired cats); this disorder has also been reported in a miniature Poodle. Fucosidosis is caused by a lack of alpha-L-fucosidase activity and has been reported in English Springer spaniels. Mannosidosis, a result of inadequate alpha mannosidase activity, has been described in Persian, domestic shorthaired, and domestic longhaired cats. Mucopolysaccharidosis type I (alpha-L-iduronidase deficiency) and type VI (arylsulfatase B deficiency) have been reported primarily in cats. Type I, or Hurler's syndrome, has been described in domestic shorthaired cats, as well as mixed-breed and Plott hound dogs. Type II, or Maroteaux-Lamy syndrome, has been reported in Siamese and domestic shorthaired cats, as well as the miniature Pinscher. A

number of glycogen storage diseases, or glycogenoses, have been described, most of which do not result in encephalopathic signs. Glycogenosis type IV, due to a deficient glycogen debranching enzyme, does involve the CNS, and has been described in Norwegian Forest cats. Mucopolysaccharidosis II (N-acetylglucosamine-1-phosphotransferase deficiency) has been reported in domestic shorthaired cats. Ceroid lipofuscinosis (CL) is unique in several aspects, one of which is the lack of identification of a specific lysosomal enzyme deficiency. Though the missing/defective lysosomal enzyme in CL has not been identified, the storage product is primarily composed of subunit c of mitochondrial ATPase. Ceroid lipofuscinosis has been described in two Siamese cats, but is primarily a canine disorder. Dog breeds reported with ceroid lipofuscinosis include English setter, Border collie, Dachshund, Chihuahua, Saluki, Tibetan terrier, Queensland blue heeler, Australian cattle dog, Cocker spaniel, Dalmatian, Yugoslavian sheepdog, and terrier crossbreed. A glycoproteinosis (alpha-glucosidase deficiency) called Lafora's disease has been reported in the Bassett hound, Beagle, Poodle, and mixed-breed dogs.

- b. Animals affected by lysosomal storage diseases are typically normal at birth, and develop a progressive multifocal to diffuse encephalopathy within the first several weeks to several months of life. Organomegaly (e.g., hepatomegaly, splenomegaly) is apparent upon physical examination for many of these diseases, due to accumulation of storage products in cells of the abdominal organs.

For the majority of these disorders, clinical signs of cerebellar dysfunction (e.g., intention tremor) are often evident early in the disease course. Dogs with Lafora's disease typically develop clinical signs of forebrain dysfunction (seizures, dementia) within the first year of life. Some patients with lysosomal storage disease may also exhibit signs of a myelopathy, polyneuropathy, and/or a myopathy. In some cases of GCL, pelvic limb ataxia is the first obvious neurologic abnormality. Skeletal abnormalities (e.g., craniofacial malformation, joint immobility) are a common feature in the mucopolysaccharidoses, mannosidosis, and mucopolysaccharidosis II. Pelvic limb paresis often develops in cases of mucopolysaccharidoses and mucopolysaccharidosis, due to impingement of the spinal cord by bony vertebral growths into the vertebral canal. Norwegian Forest cats with glycogenosis type IV may exhibit seizure activity, deficient menace responses, abnormal proprioceptive responses, and dysphagia, in addition to generalized weakness (due to neuromuscular dysfunction).

Two of the storage disorders, fucosidosis and ceroid lipofuscinosis (CL), do not follow the typical clinical pattern of the majority of these diseases. Although the age range for onset of neurologic dysfunction in fucosidosis is 4–24 mo, the majority of dogs begin to exhibit signs of an abnormality between 12 and 18 mo of age. Early in the disease course,

clinical signs of forebrain dysfunction predominate in fucosidosis (e.g., behavior change, circling). The disease progresses over 2–3 yr to include clinical signs such as ataxia, dysphagia, vision and hearing loss, nystagmus, and dysphonia. Enlargement of the ulnar nerves is often palpable in dogs with fucosidosis. The enlargement is due to both edema and infiltration of the nerves with lipid-filled phagocytes and Schwann cells. Encephalopathic signs of ceroid lipofuscinosis initially manifest at a wide age range (6 mo to 8 yr), most often beginning at 1–2 yr of age. Behavior changes and visual deficits are typically the first abnormalities noticed. The disease typically progresses over one to several years to include neurologic abnormalities such as seizures, ataxia, tremors, and hypermetric gait. Both cats reported with CL exhibited rapid deterioration of neurologic status.

- c. Tentative diagnosis of a lysosomal storage disease is based upon clinical signs of a progressive, multifocal/diffuse encephalopathy in a young animal, especially in a susceptible breed. Cerebrospinal fluid analysis is usually normal but may reveal increased protein levels with a normal cell count. Computed tomographic or magnetic resonance imaging of the brain of dogs with ceroid lipofuscinosis may reveal abnormalities, such as ventriculomegaly, brain atrophy, and abnormal brain-tissue density (Fig. 4.1). Definitive diagnosis can be achieved, depending on the specific disease process, by demonstrating deficient lysosomal enzyme activity and/or a storage product in leukocytes or cultured cells (e.g., skin fibroblasts), by demonstrating storage material via histology of biopsied tissue or tissue

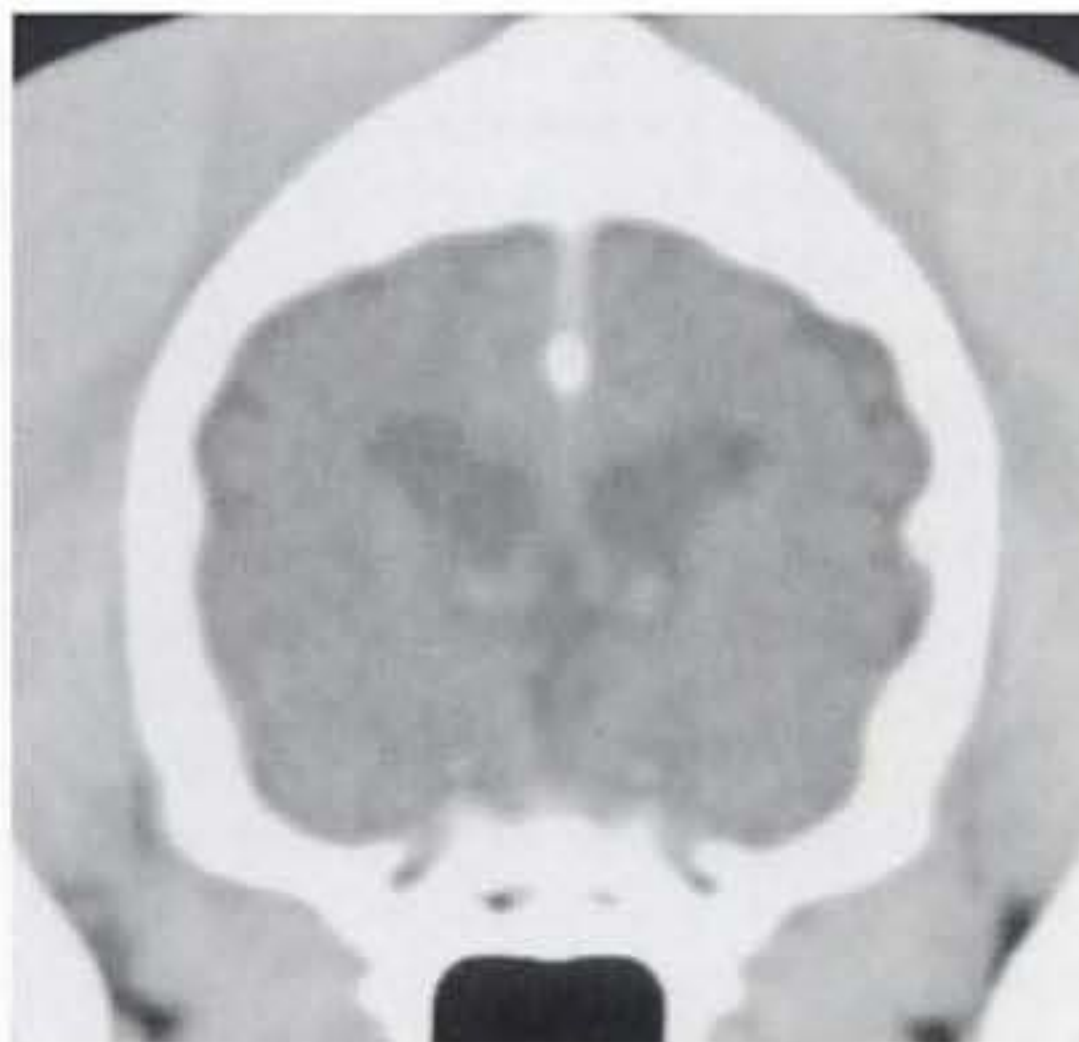


Fig. 4.1. CT image (transaxial view) of the brain of a dog with ceroid lipofuscinosis. Mild ventriculomegaly and cerebral cortical atrophy are evident (Courtesy of Dr. Mike Walker).

- obtained postmortem (using special stains), or by electron microscopic (EM) evaluation of affected tissue. In some storage disorders, the storage product is excreted in the urine and can be identified via a urine sample.
- d. At present, the prognosis for the lysosomal storage disorders in dogs and cats is grave. For the majority of these disorders, affected animals are euthanized due to progressively worsening neurologic dysfunction within the first year of life. For the more slowly progressive disorders (i.e., fucosidosis, ceroid lipofuscinosis), continuous neurologic dysfunction leads to death or euthanasia usually within 1–2 yr of diagnosis. Despite the poor outlook for lysosomal storage disorders, bone marrow transplantation and parenteral lysosomal enzyme replacement therapy have been successful in some human and some animal lysosomal storage disorders. Gene transfer therapy is also being actively investigated and will hopefully be available in the future.
2. Leukodystrophy/spongy degeneration^{1–3,18,19}
 - a. The leukodystrophies are thought to be due to abnormal synthesis (by oligodendrocytes) and/or maintenance of myelin in the central nervous system. This is a diverse group of rare, poorly understood, suspected heritable, progressive diseases. Some of these diseases produce clinical signs of a myelopathy rather than encephalopathy, and are discussed elsewhere (see Chapter 9). Leukodystrophy/spongy degeneration of the brain has been described as primarily affecting the white matter in Labrador retrievers, Dalmatians, Silkie terriers, Samoyeds, Shetland sheepdogs, a Scottish terrier, a miniature Poodle, and Egyptian Mau cats. Primarily gray matter spongy degeneration has been described in Bull Mastiffs, Salukis, Malinois/Shepherd mixed-breed dogs, and Cocker spaniel littermates.
 - b. Neurologic dysfunction typically begins within the first 6 mo of life, and progressively worsens. Clinical signs are variable, depending upon breed, but may include visual deficits, behavior changes, obtunded mental status, seizures, cerebellar dysfunction (tremors, ataxia), dysphagia, paraparesis, and tetraparesis. Similar to lysosomal storage diseases, a multifocal/diffuse disorder may be evident.
 - c. Tentative diagnosis is based upon typical clinical signs of dysfunction in a breed previously reported with leukodystrophy/spongy degeneration. Since these are progressive, fatal diseases, definitive diagnosis is based upon postmortem histologic findings of extensive CNS white matter loss, often with attendant vacuolation of the brain tissue (spongiform change). In some cases (e.g., Scottish terrier, miniature Poodle), astrocytic inclusion bodies, referred to as Rosenthal fibers, are identified. These latter cases have been termed fibrinoid leukodystrophy and are similar to a leukodystrophy in people called Alexander's disease. Histopathologic findings in Shetland sheepdogs are reminiscent of another human leukodystrophy called Canavan's disease.

- d. There is no treatment for leukodystrophy/spongy degeneration of the brain. The prognosis is grave.
- 3. Neuronal vacuolation in Rottweilers²⁰⁻²²
 - a. Recently, a progressive, multifocal degenerative CNS disorder of unknown etiology was described in young Rottweilers. The hallmark of this disease is the histopathologic finding of intraneuronal vacuoles primarily in the brain stem, cerebellum, and spinal cord gray matter. The vacuoles are reminiscent of scrapie-associated spongiform change, but there is no evidence for an infectious cause for this disease.
 - b. Affected puppies typically exhibit generalized weakness and ataxia (especially in the pelvic limbs) at six to eight weeks of age. Clinical signs progress over several weeks to include worsening of the paresis, laryngeal and pharyngeal dysfunction, and behavioral changes (in some dogs). Proprioceptive placing reactions are abnormal, but spinal reflexes remain intact.
 - c. A tentative diagnosis is based upon the typical clinical signs and progression in a young Rottweiler. A definitive diagnosis is based upon histopathologic identification of neuronal vacuolation in multiple areas of the CNS.
 - d. There is no treatment for this progressive disorder. The prognosis is grave.
- 4. Multisystem neuronal degeneration/abiotrophy in Cocker spaniels^{1-3,23}
 - a. A number of breeds have been described with suspected neuronal abiotrophy. Abiotrophy refers to premature death of cells, presumably due to the lack of some factor necessary for cellular survival. Most of the abiotrophies described cause signs primarily or exclusively related to cerebellar dysfunction. A group of related, red-haired Cocker spaniels has been described with suspected neuronal abiotrophy. These dogs exhibited signs of both forebrain and cerebellar dysfunction.
 - b. The reported dogs developed clinical signs of neurologic dysfunction at approximately 1 yr of age. The clinical signs reflect both forebrain and cerebellar dysfunction and include behavior change, generalized seizures, intention tremor, ataxic and hypermetric gait, circling, vision loss, and proprioceptive deficits. The disease progresses slowly over several months.
 - c. Tentative diagnosis is based on clinical signs of a progressive multifocal/diffuse encephalopathy in a Cocker spaniel dog. Definitive diagnosis is attained histopathologically. Widespread neuronal cell loss is evident throughout the brain in affected dogs.
 - d. Although this disorder is slowly progressive, there is no treatment and the prognosis is grave.
- 5. Cognitive dysfunction syndrome (CDS)²⁴⁻³³
 - a. An age-related syndrome similar to Alzheimer's disease (AD) in people occurs in elderly dogs and cats. Similar to AD of people, the pathophysiology of CDS is uncertain. There are pathologic similarities between the

brains of humans with AD and dogs and cats with CDS. Cerebral vascular changes, meningeal thickening, gliosis, and ventricular dilatation occur in brains of both AD and CDS patients. More specifically, the progressive accumulation of a neurotoxic protein called beta-amyloid in the brain (in and around neurons) is a consistent feature in both AD and CDS. These accumulations coalesce to form plaques (neuritic plaques) and are most prominent in the frontal cerebral cortex and in the hippocampus in both human and veterinary disorders. In both disorders, the degree of beta-amyloid accumulation correlates with the extent of cognitive impairment.

Neurochemical changes that occur in the aging brain are thought to contribute to progressive cognitive impairment. These include decreased levels of acetylcholine (brain levels of acetylcholinesterase increase with age), norepinephrine, and dopamine, and increased levels of damaging free radicals. Brain monoamine oxidase B (MAOB) activity is consistently elevated in AD patients. Since MAOB catalyzes the breakdown of dopamine (with subsequent formation of free radicals), it may play a central role in the neurochemical changes leading to cognitive impairment in AD and CDS.

- b. Cognitive dysfunction syndrome is recognized primarily in elderly dogs (more than 9 yr) and cats (more than 12 yr), but should be suspected in animals 7 yr or older that are demonstrating progressive cognitive impairment. Clinical signs of CDS are numerous and often nonspecific. They include inattentiveness, inactivity, aimless wandering (often pacing at night), demented behavior, disturbance of the sleep/wake cycle, urinary and/or fecal incontinence, difficulty navigating stairs, becoming lost in previously familiar environments, failure to recognize previously familiar people or animals, decreased interaction with family members, hearing loss, and excessive vocalization (often at night). Cats with CDS occasionally exhibit overresponsive and aggressive behavioral patterns. Owners of CDS pets often describe their pets as acting "senile."
- c. Similar to AD of people, a diagnosis of CDS in a dog or cat is based primarily on historical complaints indicative of progressive cognitive impairment. Before arriving at a presumptive diagnosis of CDS, the clinician should rule out other potential causes of cognitive dysfunction, such as metabolic disorders (e.g., hepatic encephalopathy) and structural brain disorders (e.g., brain tumor). In AD, CT or MR imaging of the brain is usually performed as part of the diagnostic workup, and should ideally be part of the diagnostic plan for CDS patients. Brain imaging of AD patients can be normal, but may reveal brain atrophy, ventricular enlargement, and lesions in the medial temporal lobes of the cerebral cortex.
- d. There is no known cure for CDS. The use of oral L-deprenyl (selegiline), an irreversible inhibitor of MAOB, has been demonstrated to improve cognitive function and slow progression of the disease in the majority of dogs and cats with CDS. There is considerable variability in the degree of

response achieved among patients, however. L-deprenyl is thought to exert its beneficial effects in the brain by restoring dopaminergic balance, as well as enhancing catecholamine levels, and decreasing levels of damaging free radical species. The dosage for dogs is 0.5–1.0 mg/kg every 24 hr. Cats are administered 0.5 mg/kg every 24 hr. Most patients will exhibit a positive response within the first month of therapy. Other drugs with some therapeutic potential for CDS include propentofylline and nicergoline.

Progression of CDS appears to be more rapid in castrated versus intact male dogs, suggesting a potential role for hormone replacement therapy in this disease. The prognosis for CDS is guarded. Most affected patients are euthanized within 18–24 mo of onset of clinical signs, either due to progressive cognitive impairment or unassociated medical problems.

B. Anomalous/developmental

1. Congenital hydrocephalus^{34–54}

- a. The phenomenon of excessive CSF in the ventricular system of the brain occurs commonly in young dogs, especially of the toy and brachycephalic breeds, and less commonly in cats. Congenital hydrocephalus may be an autosomal recessively inherited trait in the Siamese cat. The list of potential causes for congenital hydrocephalus (i.e., evident from birth) is diverse and extensive, and involves disturbances to the developing fetus or the neonate, including the following: intraventricular hemorrhage (e.g., dystocia-related); viral infections (e.g., parainfluenza virus in dogs, coronavirus in cats); teratogen exposure; nutritional deficiencies (e.g., vitamin A); and heritable malformations. Ventriculomegaly results from obstruction of CSF flow within the ventricular system (e.g., mesencephalic aqueduct stenosis) and/or insufficient absorption of CSF into the venous system at the arachnoid villi level.

It is the rule, rather than the exception, that a specific cause for congenital hydrocephalus is not apparent at the time of clinical presentation; this lack of an active causative process (e.g., inflammation, hemorrhage) helps define this form of hydrocephalus. Hydrocephalus, especially if progressive, can cause neurologic dysfunction from compression and stretching of brain parenchyma, as well as from brain ischemia and interstitial edema. Many animals, especially of the predisposed breeds, have hydrocephalus based upon ventricular enlargement, yet have no discernible neurologic dysfunction. There is no correlation between extent of ventricular enlargement and clinical signs of disease.

In this text, a patient is considered to have congenital hydrocephalus only if all three of these criteria are met: (1) ventriculomegaly is demonstrated; (2) there is no active, potentially causal disease process identifiable; and (3) the patient exhibits clinical signs of brain dysfunction. Hydrocephalus may exist concurrently with other anomalous conditions

that affect the CSF pathways, such as Dandy-Walker syndrome, Chiari malformations, and syringomyelia/hydromyelia.

- b. Dogs and cats with congenital hydrocephalus typically are presented for signs of neurologic dysfunction within the first 6 mo of life. The rate of clinical progression of congenital hydrocephalus is highly variable, and a considerable proportion of hydrocephalic animals may not develop clinical signs of encephalopathy until adulthood. Common physical characteristics of hydrocephalic patients include a large, dome-shaped head, open fontanelles or larger calvarial defects, and bilateral ventrolateral strabismus (Fig. 4.2). The strabismus may be due to orbital skull malformations, rather than to vestibular dysfunction. Clinical signs of neurologic dysfunction usually reflect a forebrain disorder and include obtundation, behavior abnormalities, circling, pacing, and seizure activity. Some hydrocephalic patients may also exhibit vestibular and/or cerebellar dysfunction.
- c. Diagnosis of congenital hydrocephalus is based upon a combination of characteristic clinical features, demonstration of ventriculomegaly, and the absence of other causes of encephalopathy. Ultrasonography (through open fontanelles or calvarial defects) and advanced imaging (CT/MRI; Fig. 4.3) have largely supplanted more invasive methods of documenting ventriculomegaly (e.g., contrast ventriculography). Electroencephalography (EEG) has been used historically to assist in the diagnosis of congenital hydrocephalus, with affected patients typically exhibiting slow frequency, high-voltage activity. However, these EEG findings are relatively nonspecific, and seldom contribute much to the diagnosis of congenital hydrocephalus.
- d. Medical treatment of congenital hydrocephalus is aimed at reduction of CSF production. Oral prednisone, at an initial dosage of 0.25–0.50



Fig. 4.2. Dog with congenital hydrocephalus, demonstrating typical physical characteristics (Courtesy of Dr. Joan Coates).

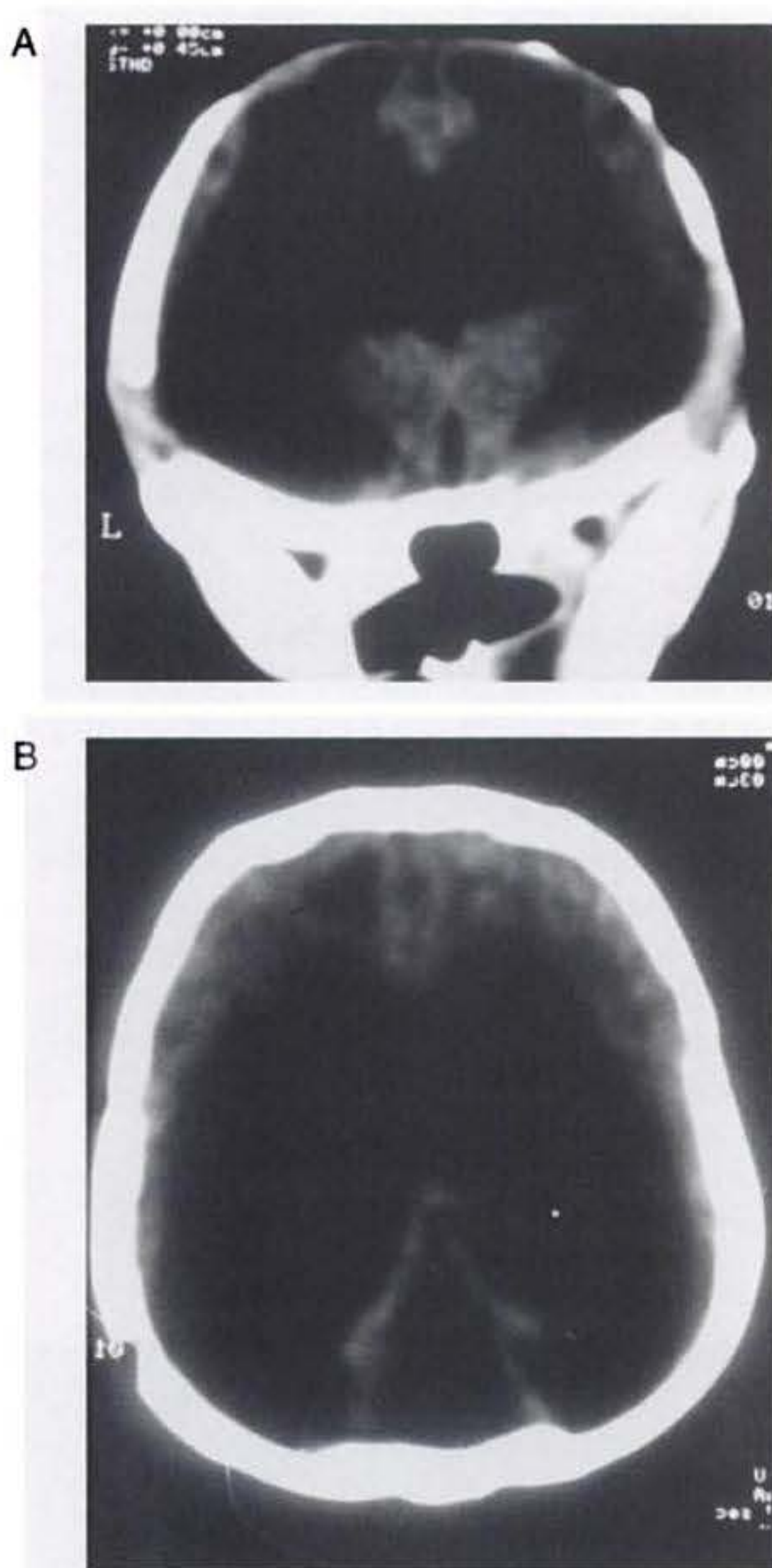


Fig. 4.3. Transaxial (A) and dorsal (B) CT brain images demonstrating severe congenital hydrocephalus in a dog.

mg/kg q12 hr, may decrease CSF production. Prednisone should be reduced over several weeks to the lowest possible dosage required to control clinical signs. Oral acetazolamide, a carbonic anhydrase inhibitor, may also be used on a short-term basis to decrease CSF production. The

dosage for acetazolamide is 10 mg/kg q6–8 hr. Prolonged acetazolamide use, especially in conjunction with glucocorticoids, may result in severe potassium depletion. The use of the proton pump inhibitor omeprazole may hold some promise as a means to decrease CSF production in congenital hydrocephalus patients. Anticonvulsant drugs are administered if the patient is experiencing seizure activity.

The goal of surgical treatment of hydrocephalus is to continually divert excessive CSF from the ventricles of the brain to either the peritoneal cavity or the right atrium of the heart. Both ventriculoatrial and ventriculoperitoneal shunts have been successfully placed in dogs with congenital hydrocephalus. Ventriculoperitoneal shunt placement is technically more feasible than ventriculoatrial shunt placement, especially in very small patients (Fig. 4.4).

The prognosis for dogs and cats with congenital hydrocephalus is variable, but is generally guarded. Medical therapy may be effective in some patients, whereas others require surgical shunting procedures for long-term control of clinical signs.

2. Dandy-Walker syndrome^{34,53,54}

This is a developmental malformation described in dogs and one cat. The most striking abnormality is the partial or complete lack of a cerebellar vermis. Cystic dilation of the fourth ventricle, hydrocephalus, and other malformations of the brain and spinal cord often accompany the vermal defects. This disorder leads primarily to cerebellar dysfunction and is discussed in more detail in Chapter 8.

3. Intracranial intra-arachnoid cyst (IIAC)^{55,56}

- a. Cystic structures located in the caudal fossa were recently described in six dogs. Five of these were associated with the quadrigeminal cistern, and



Fig. 4.4. Lateral radiograph of a dog with a ventriculoperitoneal shunt placed.

one was located at the cerebellomedullary angle. A similar structure was reported in a 1-yr-old cat, based upon MR imaging of the patient. The author has also observed a similar cystic condition in a kitten. This disorder is believed to represent a developmental abnormality of the intracranial ventricular system and may occur concurrently with other abnormalities (e.g., congenital hydrocephalus). The cyst may or may not communicate with the remainder of the ventricular system.

- b. Three of the six reported dogs were less than 1 year of age at clinical presentation, but one was 4 yr old, and two were 7 yr old. In human beings with IIAC, there is a similar predominance of younger patients (less than 20 yr old), but middle-aged and elderly patients are encountered. Five of the six dogs were of small breeds. Generalized seizure activity was a common clinical feature in the reported cases, but other signs of forebrain and brain-stem dysfunction were evident in some dogs.
 - c. Diagnosis in a patient with signs of intracranial disease is based primarily upon imaging via CT or (preferably) MRI. The characteristic appearance of IIAC is a well-demarcated circular structure containing fluid isointense with CSF (Fig. 4.5). Concurrent inflammatory brain disease must be ruled out (i.e., CSF examination), as IIAC may be an incidental finding.
 - d. Treatment of patients with IIAC may consist of medical therapy alone (e.g., glucocorticoids, diuretics, anticonvulsants) or medical therapy combined with surgery. Surgical therapy in people with these cysts involves either cutting a window into the cyst for drainage (fenestration) or shunting, as described in congenital hydrocephalus. The latter procedure addresses concomitant hydrocephalus in patients with both ventricular anomalies. Fenestration of intracranial intra-arachnoid cysts was performed successfully in two of the reported dogs. Although data are currently limited, the prognosis for this condition may be favorable with appropriate treatment.
4. Neuronal migration disorders—lissencephaly/pachygyria and polymicrogyria^{34,38,57,58}
- a. These are uncommon, probably heritable disorders thought to be due to abnormal cerebral cortical neuronal migration during fetal development. Lissencephaly/pachygyria is characterized by reduced numbers or absence of gyri on the surface of the cerebral hemispheres and an abnormally thickened, histologically disorganized (loss of the normal laminar arrangement) cerebral cortex. This disorder is most commonly encountered in the Lhasa Apso breed, but has also been described in the Wire-haired Fox terrier, Irish setter, and Korat cat. In Irish setters, cerebellar hypoplasia and dysplasia occur concurrently. Polymicrogyria is characterized by excessive, small gyri on the cerebral cortex. This condition was described in a group of four related standard Poodles that also displayed asymmetric dilation of the lateral ventricles. Disorganization of the cerebral cortex was also evident histologically in these standard Poodles.

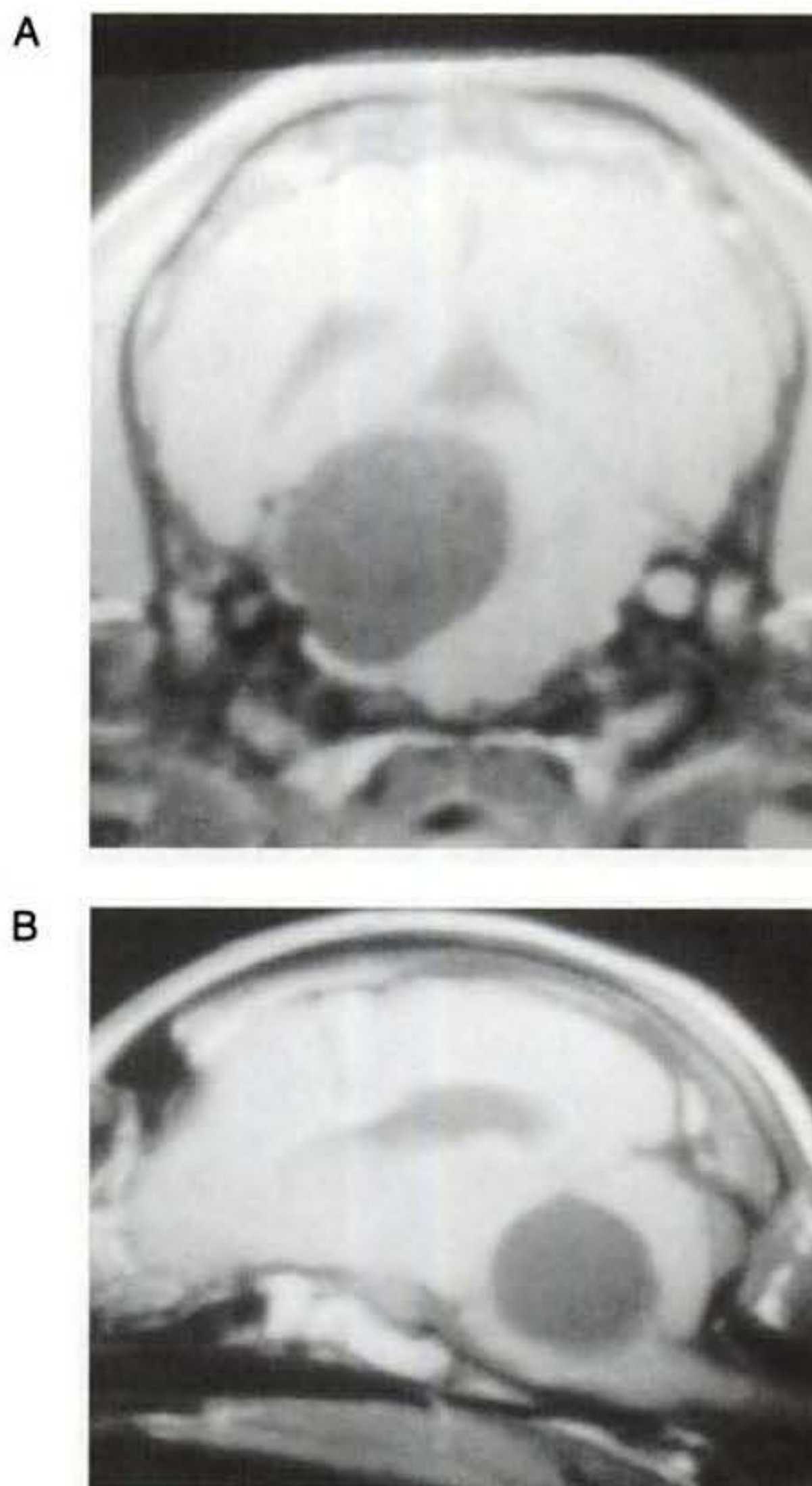


Fig. 4.5. Transaxial (A) and sagittal (B) MR images of a dog with an intracranial intra-arachnoid cyst.

- b. Clinical signs associated with these neuronal migration disorders are typically evident within the first several months of life. Animals with lissencephaly/pachygyria may have behavioral abnormalities and seizure activity, and may be difficult to train. The dogs reported with polymicrogyria and ventriculomegaly exhibited blindness as the major clinical abnormality. Other clinical signs included a hypermetric gait in three of four dogs, and seizures in one dog.
- c. The diagnosis of these disorders is tentatively based upon characteristic clinical signs in a susceptible breed. Diagnosis may be aided by advanced



Fig. 4.6. T2-weighted MR image (transaxial view) of a lissencephalic dog's brain. Note the absence of sulci on the cerebral surface (Courtesy of Dr. Gregg Kortz).

imaging (Fig. 4.6). Although it has not yet been investigated thoroughly in dogs and cats, MR imaging is used to diagnose children with these disorders, and would be preferable to CT in demonstrating abnormal gyral architecture of the cerebral cortex. Computed tomography and MRI revealed asymmetric ventricular dilation in three of four standard Poodles with polymicrogyria. Definitive diagnosis of neuronal migration disorders depends upon gross and histopathologic findings of the brain via biopsy or at necropsy.

- d. Neuronal migration disorders are nonprogressive, nonfatal diseases. While there are no treatments for these disorders, animals with lissencephaly/pachygyria may be acceptable pets, if provided the appropriate home environment. Seizures can be controlled with anticonvulsant medication (see Chapter 6). The same may be true for animals with polymicrogyria; however, the only dogs reported to date with this disorder were euthanized at an early age.
- 5. Miscellaneous malformations^{34,38,59,60}
 - a. There are a number of rarely reported malformations of the brain, most of which are not compatible with life. Exencephaly is protrusion of brain tissue through a calvarial defect without a meningeal or skin covering. Meningoencephalocele refers to a similar protrusion that maintains both meningeal and skin coverings. Hydranencephaly describes the absence or near absence of cerebral cortical tissue, and may be difficult to discern from very severe hydrocephalus. Anencephaly is the total or partial absence of brain tissue and calvarium. Porencephaly is a condition characterized by cystic cavities in the cerebrum, which may communicate with the ventricular system. Holoencephaly, or holoprosencephaly, describes a single, nondivided cerebrum. Cyclopic malformation refers to the development of a single, median-positioned eye. Chiari malformation (Type I)

is a malformation of the occipital region that leads to a small caudal fossa with cerebellar herniation and compression of the brain stem at the cervicomedullary junction. Epidermoid cysts have been reported in the cerebellomedullary angle region of dogs of various ages. Numerous etiologies have been proposed for these disorders, including heritable defects, infectious agents, toxin exposure, and nutritional imbalances. Meningoencephaloceles have been described in Burmese kittens as part of a heritable craniofacial malformation syndrome. Feline parvovirus (panleukopenia virus) has been implicated as a cause of hydranencephaly and porencephaly in kittens. Agenesis of the corpus callosum and cyclopiian malformation have been described in kittens exposed to griseofulvin during gestation. Exencephaly may occur when kittens are exposed to griseofulvin, methylmercury, or hydroxyurea during gestation.

- b. Dogs and cats with these miscellaneous brain malformations are usually either stillborn or die or are euthanized shortly after birth. Malformations compatible with life include epidermoid cysts and Chiari Type I malformation. Epidermoid cysts are usually diagnosed in mature dogs, usually young adults. A condition similar to Chiari Type I malformation has been described in dogs in association with syringomyelia/hydromyelia (see Chapters 8 and 9). Most dogs with “Chiari-like” malformations are responsive to medical and surgical therapy. There are no effective treatments for the majority of these disorders and the prognosis is usually guarded to poor.

C. Metabolic

Because the brain has extremely high metabolic demands, systemic abnormalities that interfere with normal energy metabolism of the central nervous system may result in clinical signs of encephalopathy. Since the cerebral cortical neurons are most susceptible to altered energy metabolism, most of these metabolic diseases lead to signs of forebrain dysfunction. If not corrected, however, brain-stem dysfunction and ultimately death of the patient can result from some metabolic diseases. Patients with metabolic encephalopathy tend to have symmetric clinical signs. In general, alleviating or eliminating clinical signs of encephalopathy in patients with the following disorders depends primarily on treatment of the underlying metabolic disease. The basic treatment strategies for these underlying diseases are discussed, but an in-depth discussion of specific therapies for these metabolic conditions is beyond the scope of this text.

1. Hepatic encephalopathy⁶¹⁻⁷⁷

- a. A major function of the liver is to filter out potentially toxic substances received from the gastrointestinal tract (via the portal venous system) so that these substances do not gain access to the general circulation. When this function is compromised due to either hepatic failure or portosystemic shunting, or both, clinical signs of encephalopathy may result. The pathogenesis of hepatic encephalopathy is complex. Proposed causative

factors include gut-derived toxins, such as ammonia, skatoles, indoles, and short-chain fatty acids, that reach the systemic circulation and cause neurotoxicity; alteration in brain neurotransmitter balance and/or production of "false neurotransmitters" due to increased circulating levels of aromatic amino acids; and circulating benzodiazepine-like substances that act on brain gamma-aminobutyric acid (GABA) receptors.

Most cases of hepatic encephalopathy are due to congenital portosystemic shunts (PSS), which are aberrant vascular communications between the portal and systemic venous systems (i.e., bypassing the liver). The majority of these shunts are extrahepatic (located outside the liver parenchyma) versus intrahepatic (within the liver parenchyma). Extrahepatic shunts typically occur in small and toy breeds of dogs (e.g., Yorkshire terriers, miniature Schnauzers) and less commonly in cats, whereas intrahepatic shunts are more common in larger dog breeds (e.g., Labrador retrievers, Irish Wolfhounds). Multiple acquired extrahepatic shunts can form as a result of chronic portal hypertension in dogs and cats with longstanding hepatic disease.

A congenital disorder termed hepatic microvascular dysplasia (HMD) was recently described in which there are suspected to be multiple microscopic shunting vessels within the liver that bypass the hepatic sinusoidal system, rather than a grossly visible anomalous vessel. This appears to be most common in small and toy breeds of dogs (e.g., Cairn terriers may be predisposed) and cats. Animals with PSS may also have HMD concurrently. Other causes of hepatic encephalopathy include congenital arteriovenous fistulas, and acquired hepatic disorders (e.g., toxin-induced, infectious, chronic active hepatitis, neoplasia).

- b. Clinical signs of hepatic encephalopathy include obtunded mental status, abnormal behavior, compulsive pacing, head-pressing, visual deficits, and seizure activity. Other clinical signs consistent with hepatic failure (e.g., weight loss or failure to gain weight, anorexia, vomiting, diarrhea, PU/PD) are often present. Cats with PSS are more likely to seizure than dogs, and often exhibit ptyalism as a characteristic clinical sign. Patients with PSS usually develop clinical signs associated with hepatic insufficiency within the first year of life, but adult animals are occasionally encountered. Dogs and cats with HMD (without PSS) and acquired hepatic disorders are more likely to develop clinical signs as adults (over 1 yr).
- c. Diagnosis of hepatic encephalopathy is based upon documenting hepatic dysfunction in a patient with neurologic deficits typical of a metabolic encephalopathy. Bloodwork abnormalities (microcytic red blood cells, low blood urea nitrogen [BUN], low albumin, etc.) often point to a liver problem. Liver enzymes (e.g., alanine aminotransferase-ALT, serum alkaline phosphatase-SAP) are typically normal to slightly elevated in PSS and HMD patients, but are often elevated in acquired hepatic disorders. Ammonium biurate crystals may be evident on urinalysis in PSS patients.

Liver function tests, such as serum bile acid and ammonia levels are often abnormally elevated.

Although there are multiple methods (e.g mesenteric portography, abdominal ultrasound) available to demonstrate the existence of PSS, the preferred method is per-rectal scintigraphy. A radioactive compound called technetium (^{99m}Tc) is administered rectally, and the patient is placed under a gamma camera to measure radiation activity as the substance is absorbed from the colon. If the radioactivity is first detected in the heart and lungs, rather than the liver, this indicates the presence of PSS (Fig. 4.7).

Animals with HMD may be difficult, if not impossible, to diagnose without a liver biopsy. These patients tend to have normal or slightly abnormal bloodwork abnormalities compared to PSS patients (e.g., serum albumin and cholesterol levels, mean corpuscular volume). Also, serum

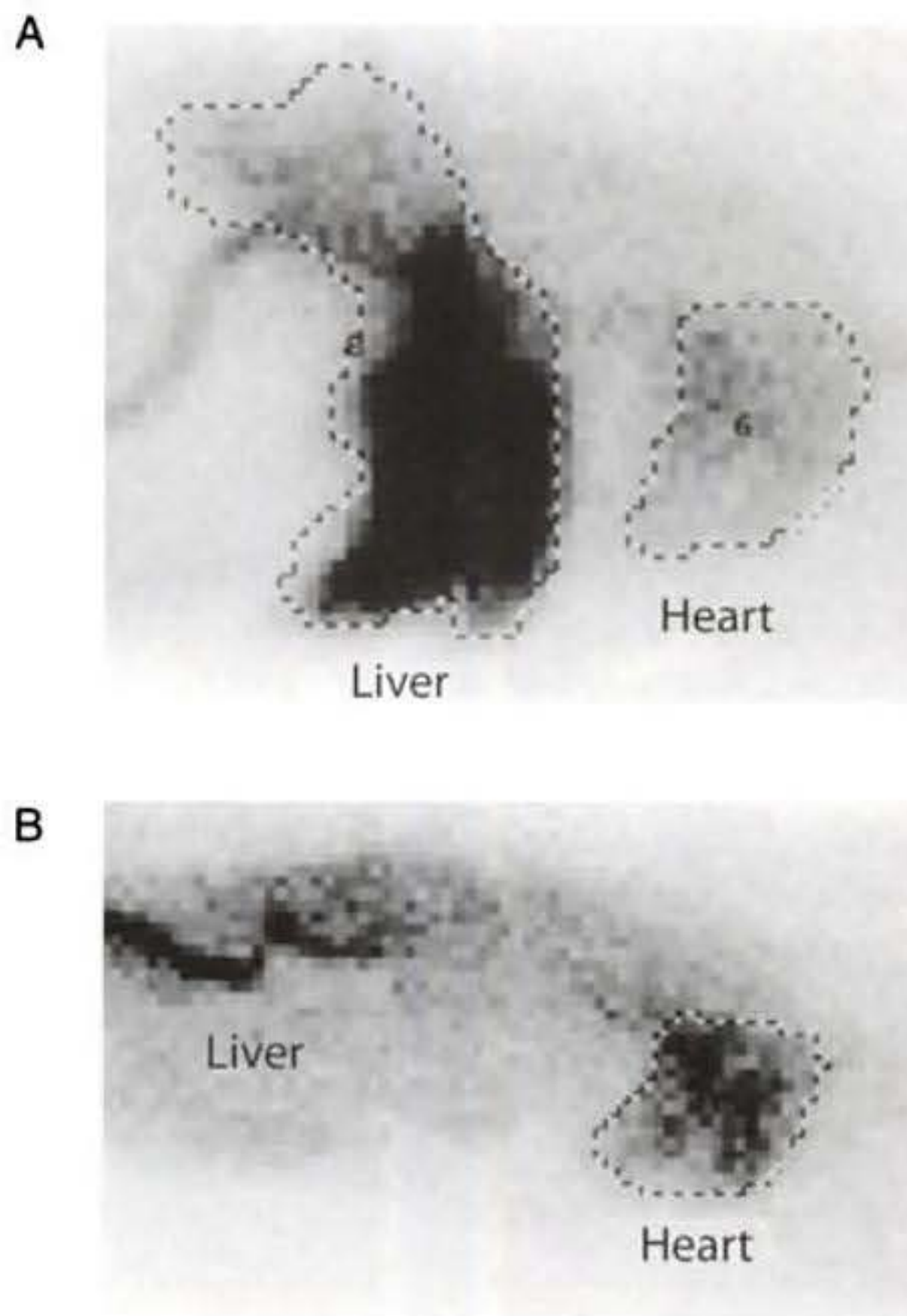


Fig. 4.7. Normal (A) and abnormal (B) per-rectal scintigraphy studies in dogs. Note the lack of radioactivity in the liver of the dog with a PSS (B) compared to the liver of a normal dog (A) (Courtesy of Dr. Anne Bahr).

bile acid concentrations in HMD patients, especially postprandial, tend to be lower than in patients with PSS. Per-rectal scintigraphy results are also normal in animals with HMD. Other hepatic disorders also typically require liver biopsy for a diagnosis.

- d. Treatment for hepatic encephalopathy is directed at reducing the level of gut-derived toxins and controlling seizures, if present. A diet with a low amount of high-quality protein (e.g., K/D diet) is usually instituted to minimize ammonia production by gut bacteria. Oral medications such as lactulose, a synthetic disaccharide, with or without oral antibiotics (e.g., aminoglycosides), are administered, to decrease colonic bacterial production of volatile fatty acids and other potentially neurotoxic substances. Lactulose is hydrolyzed by colonic bacteria to produce organic acids (e.g., lactic, acetic, formic acid) and carbon dioxide. The organic acids lower the pH of the colon, trapping colonic ammonia in the form of nonabsorbable ammonium. Lactulose may also lead to a favorable alteration of the colonic flora, accelerated intestinal transit time, and may exert some antiendotoxin activity. Lactulose is administered at an initial dose of 0.5–1.0 ml/kg body weight, every 8 hr. The dose is adjusted, if necessary, to result in two to three soft stools per day. Neomycin sulfate is poorly absorbed when administered orally, but is active against urea-splitting bacteria in the colon. The dose of neomycin is 20 mg/kg body weight, every 8 hr. Oral ampicillin (22 mg/kg body weight, q 8 hr) and metronidazole (7.5 mg/kg body weight, q 8 hr) are also commonly administered to hepatic encephalopathy patients, for their effects on colonic flora, and as protection against sepsis.

In severely encephalopathic patients, dilute betadine and/or lactulose enemas may be instituted. A lactulose enema is prepared using three parts lactulose to seven parts of water. The enema is administered at a dose of 20 ml/kg and retained in the colon for 15–20 min. This is repeated every 4–6 hr, if necessary. Some patients with hepatic insufficiency may be hypoglycemic and need supplemental parenteral glucose. It is important to prevent or reverse conditions that may exacerbate hepatic encephalopathy, such as alkalosis, hypokalemia, and gastrointestinal hemorrhage.

Anticonvulsant medication needs to be tapered to the individual patient, and generally administered at lower than standard dosages if metabolized by the liver. Potassium bromide (KBr), which is renally excreted, may be the ideal anticonvulsant choice in some patients with hepatic insufficiency.

Treatment of the underlying disorder in hepatic encephalopathy cases is the key to controlling signs of neurologic dysfunction. In HMD and most acquired hepatic disorders, medical management involving dietary modification, lactulose, and other medications (e.g., prednisone, anticholestatic and antifibrotic drugs for chronic active hepatitis) form the basis of treatment. For PSS, surgical attenuation of the shunting vessel(s)

is usually recommended. Shunt attenuation using a device called an ameroid constrictor is commonly practiced; the ameroid constrictor allows for progressive attenuation of the shunting vessel following placement. Some PSS patients will develop refractory generalized seizures after shunt ligation, which can be fatal. This phenomenon is suspected to be due to an abrupt decrease in brain benzodiazepine-like substances following shunt ligation.

Clinical signs of hepatic encephalopathy can often be reversed with appropriate medical therapy. The prognosis for each patient depends on the specific underlying disease responsible for the encephalopathy. Most extrahepatic PSS dogs are successfully treated surgically with partial or complete shunt attenuation. The prognosis for cats with extrahepatic PSS and both dogs and cats with intrahepatic PSS is guarded. HMD patients can be well controlled long-term with medical therapy. The prognosis for dogs and cats with other hepatic disorders is highly variable.

2. Renal-associated encephalopathy⁷⁸⁻⁸³

- a. This category of metabolic encephalopathy encompasses uremic encephalopathy (UE), dialysis dysequilibrium syndrome (DDS), and post-transplantation encephalopathy (PTE). Similar to hepatic encephalopathy, there are numerous proposed mechanisms to explain uremic encephalopathy, which include the following: circulating neurotoxins, such as high levels of parathyroid hormone (PTH), which may have a direct toxic effect on neurons in addition to secondary effects from increased extracellular calcium levels; ionic imbalances, particularly hypercalcemia, which can lead to neuronal mineralization; hyperosmolality, causing cerebral neuronal dehydration; hypertension, which may lead to tortuosity, intimal proliferation, and necrosis of cerebral vasculature; uremic vasculitis affecting cerebral blood vessels; acid-base imbalance, specifically acidosis depressing cerebral function; and uremia-induced neurotransmitter imbalance in the brain. Low-grade anemia in some renal failure patients may contribute to these aforementioned processes in producing encephalopathy.

Dialysis dysequilibrium syndrome is thought to be caused by an osmotic gradient between the brain and the extracellular fluid environment, due to overly rapid hemodialysis. The brain remains relatively hyperosmotic to the blood, perhaps due to production of intraneuronal idiogenic osmoles during the uremic state. The gradient causes the neurons to imbibe water, leading to cerebral edema.

In PTE, described in cats after renal transplantation, uncontrolled hypertension is thought to play a major causative role.

- b. Clinical signs of renal-associated encephalopathy are similar, whether due to UE, DDS, or PTE, although they tend to be most severe with the latter disorder. Abnormal mentation, ranging from obtundation (with or without signs of dementia) to coma, and seizure activity are typical abnormali-

ties. Other clinical signs may include muscle tremors, generalized weakness, and irregular respiration. The abnormal respiratory activity is thought to be due to decreased brain-stem receptivity to chemoreceptor stimulation. Other clinical signs (dehydration, nausea/vomiting, PU/PD, etc.) are reflective of renal failure.

- c. Diagnosis of renal-associated encephalopathy is based upon typical clinical signs of neurologic dysfunction in a patient with renal failure, with no other obvious cause of brain disease. Development of encephalopathic signs soon after hemodialysis or renal transplantation provides compelling evidence for DDS and PTE, respectively.
- d. Treatment of renal-associated encephalopathy depends primarily upon management of the underlying kidney disease. Electrolyte and acid-base imbalances should be corrected, if indicated, and seizures should be controlled with anticonvulsant drugs. Managing arterial hypertension in cats before and after renal transplantation with propranolol, hydralazine, and/or acepromazine may help prevent the development of PTE.

The prognosis of renal-associated encephalopathy is variable, and depends mainly on the specific renal abnormality. In most cases, the encephalopathy can be ameliorated or resolved with control of uremia. The development of PTE is best avoided, as these cats tend to have severe signs of neurologic dysfunction, and a high mortality rate.

3. Hypoglycemic encephalopathy^{61-63, 84-88}

- a. The brain has an absolute requirement for glucose. Glucose enters the brain via a noninsulin-dependent facilitated transport mechanism. This transport mechanism requires a minimum blood glucose level to operate effectively. There are limited glycogen stores in the brain and the neuronal energy depletion associated with severe (usually less than 45 mg/dl) hypoglycemia often results in clinical signs of encephalopathy.

There are multiple causes of hypoglycemia, including overproduction of endogenous insulin or insulin-like substances by pancreatic insulinomas or other neoplasms, glycogen depletion in neonatal/juvenile puppies (usually of toy/miniature breeds) and kittens, sepsis, and exogenous insulin overdose (i.e., diabetes mellitus patients, especially feline). Other less-common causes of clinically significant hypoglycemia include hypoadrenocorticism, liver failure, glycogen storage diseases, and the so-called hunting dog hypoglycemia syndrome, the latter of which may represent the combined effects of strenuous exercise with inadequate caloric intake.

- b. The nature and severity of clinical signs produced by severe hypoglycemia depend upon the rate of decline of blood glucose, the absolute degree of hypoglycemia, and the duration of hypoglycemia. Rapid decreases of blood glucose result in a systemic adrenergic response, with typical clinical signs such as pupillary dilation, tremors, irritability, vocalization, and extreme hunger. Slower decreases in blood glucose levels, as is common with insulinomas, typically result in signs of encephalopathy, such as

- behavior changes, altered mental status (typically obtundation, but coma can result if hypoglycemia is untreated), seizure activity, and visual dysfunction. Generalized weakness is also a common characteristic feature of dogs and cats with progressive hypoglycemia.
- c. The diagnosis of hypoglycemic encephalopathy is based on documenting hypoglycemia in an encephalopathic patient whose clinical signs of neurologic dysfunction improve or resolve with normalization of blood glucose levels. Specific diagnostic tests (e.g., insulin/glucose ratio for insulinoma) for the various causes of hypoglycemia are not covered in this text (consult the appropriate references listed).
 - d. Symptomatic therapy for hypoglycemic encephalopathy involves intravenous administration of 0.5–1 ml/kg of 50% dextrose, diluted 1:2 with sterile water. This may need to be repeated and/or the patient may require a continuous infusion of 5% dextrose. Concentrated dextrose solutions should be given through large-bore veins like the jugular, especially if repeated administrations are performed. Specific therapies for individual causes of hypoglycemia are covered in the references provided. The prognosis for short-term correction of hypoglycemic encephalopathy is usually excellent. The long-term prognosis varies with the underlying disease process, but is generally guarded to good. Pancreatic insulinoma, probably the most common cause of hypoglycemic encephalopathy in dogs, is associated with a mean survival time of 12–14 mo with combination surgical/medical management.
4. Electrolyte-associated encephalopathy (EAE)^{61–63,89–95}
- a. Imbalances of sodium (Na^+) and calcium (Ca^{++}) may cause clinical signs of encephalopathy, the severity of which tends to correlate directly with the rapidity of development of the particular imbalance. There are numerous potential causes for these electrolyte disturbances. Hypernatremia and hyponatremia are, for all practical purposes, synonymous with hyperosmolality and hypoosmolality, respectively. Hypernatremia can lead to shrinkage of brain parenchymal cells. A potential secondary effect of this parenchymal shrinkage is stretching and tearing of small intracranial blood vessels with resultant hemorrhage. Both intracellular dehydration and intracranial hemorrhage may contribute to brain dysfunction in the hypernatremic state. With chronic hypernatremia (more than two or three days), brain parenchymal cells will produce osmotically active intracellular substances, called idiogenic osmoles, in an attempt to compensate for the increased extracellular osmolality. Hyponatremia can result in swelling of brain parenchymal cells with subsequent brain edema. Brain parenchymal cells will compensate for chronic hyponatremia (more than two or three days) by actively extruding osmotically active intracellular components, such as potassium and amino acids. Overly rapid correction of either a chronic hypernatremic or hyponatremic state may lead to severe encephalopathic signs. In the former scenario, the encephalopathy is due

to brain edema (associated with the idiogenic osmoles), whereas in the second, it is likely due to axonal shrinkage (due to relative lack of intracellular osmolality) and subsequent demyelination in the brain stem (particularly the thalamus), similar to central pontine myelinolysis in people.

Hypercalcemia can cause decreased excitability of neuronal cell membranes, as well as direct toxic damage to neuronal intracellular energy-producing systems. Hypocalcemia may lead to increased excitability of neuronal cell membranes, as well as abnormal neurotransmission.

- b. Clinical signs of EAE typically indicate forebrain dysfunction, but can progress to involving the brain stem. Dementia, behavior changes, altered mental status (obtundation that may progress to coma), seizures, and visual deficits are likely clinical signs of EAE. Patients with hypocalcemia may also exhibit muscular tetany.
- c. Diagnosis of EAE is based upon demonstrating an abnormal electrolyte status in an encephalopathic patient that improves or normalizes upon correction of the abnormal electrolyte level.
- d. Treatment of EAE involves correction of the electrolyte disturbance, as well as investigation and potential treatment of the underlying cause for the electrolyte abnormality. Correction of hypernatremia is achieved by administering fluids that are hypoosmolar to the patient. This can be achieved via using 5% dextrose (basically free water), half-strength or normal saline, depending upon the degree and chronicity of the hypernatremia. The amount of water to administer can be calculated according to the following formula:

$$\text{Water deficit (L)} = 0.6 \times \text{lean body weight (kg)} \\ \times \text{patient's Na}^+ / \text{normal Na}^+ - 1$$

With relatively acute hypernatremia, the deficit can be corrected quickly using 5% dextrose. With chronic hypernatremia, the deficit should be corrected gradually over 48–72 hr, starting with half-strength or normal saline, eventually switching to 5% dextrose. The chronically hypernatremic patient's sodium level should not be lowered faster than 0.5 mEq/L/hr. Hyponatremia is corrected by administering sodium containing fluids such as normal or hypertonic saline (in acute, severe cases). The amount of sodium to be replenished can be calculated as follows:

$$\text{Sodium deficit (mEq/L)} = 0.6 \times \text{lean body weight (kg)} \\ \times (\text{normal Na}^+ - \text{patient's Na}^+)$$

As with chronic hypernatremia, chronic hyponatremia should be corrected slowly over 48–72 hr, raising the patient's sodium level by no more than 0.5 mEq/L/hr.

Hypocalcemia is corrected in the emergency situation by slow intravenous infusion of 10% calcium gluconate at a dosage of 5–15 mg/kg over 10–30 min; this should work out to be 0.5–1.5 ml/kg. It is extremely important not to confuse the two ways of expressing dosage of this drug, as overdosage can be fatal. While administering calcium gluconate, the patient's electrocardiogram (ECG) should be continuously recorded. The infusion should be stopped if premature ventricular contractions, shortening of the QT interval, or bradycardia are observed. Once the patient is stabilized, maintenance oral calcium and vitamin D supplementation can be initiated. Emergency therapy of the hypercalcemic patient usually involves diuresis with 0.9% saline (two to three times maintenance fluid rate) and furosemide (2–4 mg/kg intravenously, q 8–12 hr, or a 5 mg/kg IV bolus, followed by 5 mg/kg/hr continuous infusion). Other therapies may include glucocorticoids and calcitonin administration. The prognosis for reversing encephalopathic signs due to electrolyte disturbances is generally favorable. The overall prognosis for the individual patient is highly variable and depends upon the specific disease process responsible for the electrolyte aberration.

5. Miscellaneous endocrine-related encephalopathies^{61–63,96–101}
 - a. In addition to pancreatic insulinoma and disorders of the parathyroid glands, there are several endocrine disorders that can lead to brain dysfunction. Hyperthyroidism (in cats, rarely dogs), hypothyroidism (in dogs, rarely cats), diabetes mellitus, and hyperadrenocorticism may each occasionally lead to clinical signs of encephalopathy. Hyperthyroidism may cause encephalopathic signs by altering brain neurotransmitter balance; thyroid hormones may also directly increase membrane excitability of brain parenchymal cells. Systemic hypertension is a common feature of hyperthyroidism and may also contribute to encephalopathic signs. Low thyroid hormone levels in hypothyroidism may cause encephalopathy by a number of proposed mechanisms including diminished neuronal oxygen consumption, accumulation of water-retaining extracellular mucopolysaccharide substances in the brain (myxedema), and vascular compromise to the brain due to atherosclerosis of major blood vessels. Ketoacidotic and nonketotic hyperosmolar diabetes mellitus may both lead to encephalopathic signs. The pathogenesis of diabetic encephalopathy is thought to be due primarily to hyperosmolarity in both forms of the disease. Excessive circulating glucocorticoid levels in hyperadrenocorticism may lead to brain neurotransmitter imbalance; the systemic hypertension commonly associated with hyperadrenocorticism may also lead to vascular compromise of the brain.
 - b. Dogs and cats with endocrine-related encephalopathy typically exhibit signs of forebrain dysfunction in addition to other clinical signs relating to the underlying endocrine disorder (e.g., PU/PD, polyphagia, etc.). An

obtunded mental status is commonly appreciated with hypothyroidism and diabetes mellitus. Hyperthyroid cats are more likely to appear restless and irritable, and may exhibit aggressive behavior. Hyperadrenocorticoid-related encephalopathy can manifest either as obtundation or hyperexcitability. Other clinical signs of encephalopathy such as aimless pacing, focal and generalized seizure activity (rare with these endocrinopathies), and vocalization, may be appreciated in patients with these endocrine disorders. A rare yet life-threatening form of hypothyroid encephalopathy, called myxedema stupor or coma, produces severe alterations of consciousness, as the name implies. Doberman Pinschers appear to be predisposed to this syndrome.

- c. Diagnosis of an endocrine-related encephalopathy is made by documenting clinical signs of brain dysfunction in a patient with an endocrinopathy, which improve or resolve with control of the endocrine disorder. The suggested references should be consulted for specifics pertaining to diagnosis of endocrine disorders.
 - d. Treatment of endocrine-related encephalopathies involves successfully controlling the underlying endocrine disturbance. The specifics of treating each of the above-mentioned endocrinopathies is beyond the scope of this textbook. In general, severe ketoacidotic and nonketotic hyperosmolar diabetes mellitus are treated with fluid/electrolyte replacement and intravenous or intramuscular insulin administration. Hyperthyroidism is treated either by surgical removal of the hyperfunctional thyroid gland(s) or via radioactive iodine therapy. Hypothyroidism is typically treated by oral administration of thyroid replacement hormone at a dosage of 20 $\mu\text{g/kg}$ every 12 hr. Hypothyroid myxedema stupor/coma is treated via intravenous administration of thyroid replacement hormone (0.066–0.11 mg/kg) and intensive supportive care, followed by maintenance oral thyroid hormone replacement therapy. Hyperadrenocorticism is usually treated with oral lysodren, the amount titrated based on results of ACTH stimulation tests. The prognosis for endocrine-associated encephalopathies is quite variable, and depends on the underlying endocrine disorder. Except for the rare hypothyroid myxedema stupor/coma syndrome, the prognosis for both reversal of encephalopathic signs and control of the endocrine disease is typically good.
6. Encephalopathy associated with acid-base disturbances ^{61–63}
- a. Acid-base disturbances are uncommon causes of encephalopathy. There are multiple causes for the various acid-base disturbances, and the suggested references pertaining to this subject should be consulted. Of the four main types of acid-base disturbance (respiratory acidosis, metabolic acidosis, respiratory alkalosis, and metabolic alkalosis), respiratory acidosis is the most likely to cause signs of encephalopathy. Alkalosis is very unlikely to result in encephalopathic signs, and will not be discussed. Respiratory acidosis is

usually due to poor ventilatory ability, but can also occur with severe pulmonary disease. Carbon dioxide diffuses readily across the blood-brain barrier and can affect brain function in several ways. Carbon dioxide can affect the brain both directly and via decreasing brain pH levels. Carbon dioxide narcosis may occur via both alterations in brain neurotransmitter balance and increases in brain blood volume (leading to increased intracranial pressure). The hypoxia that typically accompanies hypercapnia may exacerbate the effects of hypercapnia on the brain. Metabolic acidosis may also lead to mild encephalopathic signs, but this is less likely due to the patient's ability to compensate via hyperventilation.

- b. Encephalopathy from respiratory acidosis typically results in alteration of level (obtundation to coma) and/or content (dementia/delirium) of consciousness. Such patients will also display obvious respiratory difficulty. When encephalopathic signs result from metabolic acidosis, they tend to be much less severe than those experienced with respiratory acidosis. These patients may be hyperventilating as a compensatory response, but are not usually in respiratory distress.
 - c. Diagnosis of acidosis as a cause of encephalopathy is based upon reversal of clinical signs of brain dysfunction concomitant with correction of the acid-base disturbance. The nature of the acid-base disturbance is elucidated from arterial blood-gas analysis, as well as measurements of pH and bicarbonate levels. The underlying cause for the acid-base disturbance should be investigated.
 - d. The reader should refer to the suggested references for specific treatment of acidosis. In general, bicarbonate administration and fluid replacement therapy are titrated to the individual patient's needs. Overzealous administration of intravenous bicarbonate to a patient with encephalopathy due to acidosis may cause a transient worsening of brain dysfunction. The carbon dioxide produced after administering bicarbonate to an acidotic patient will rapidly cross the blood-brain barrier, whereas the bicarbonate itself will not. This may lead to the so-called paradoxical central nervous system acidosis. If this phenomenon does occur, it is rarely of much clinical consequence. The prognosis for reversing encephalopathic signs due to acidosis is usually favorable in the short term. The overall prognosis for each patient depends upon which of the myriad possible diseases is responsible for the acid-base disturbance.
7. Mitochondrial encephalopathy (ME)¹⁰²⁻¹⁰⁶
- a. Abnormal mitochondrial respiratory enzyme function, due to a number of potentially heritable defects, is believed to be the pathophysiologic basis for a number of recently described encephalopathies and encephalomyelopathies in dogs. Progressive or episodic signs of CNS dysfunction have been reported in several breeds, most notably Alaskan huskies and Australian cattle dogs. A similar disorder has been reported in

an English Springer spaniel and was suspected (based on pathologic findings) in a Yorkshire terrier and several kittens. In addition, some of the previously described idiopathic vacuolar or spongiform encephalopathies (see degenerative diseases on page 104–105) are currently suspected to be mitochondrial encephalopathies. Clinical and pathologic findings in these animals are similar to a human disorder called Leigh's syndrome, or subacute necrotizing encephalopathy (SNE). Leigh's syndrome represents a group of heritable neurodegenerative diseases, the majority of which are due to defects in the mitochondrial respiratory enzyme chain.

- b. The majority of reported dogs initially developed clinical signs of neurologic dysfunction in the first year of life (most between 6 and 12 mo). However, there appears to be a wide age range for the onset of clinical signs. One Alaskan husky was 2.5 yr of age at onset, and another was 6 yr old. The English Springer spaniel was approximately 15 mo old at the time of onset of signs. Seizures and/or generalized ataxia of acute onset are typically the initial clinical signs. Clinical features supportive of a diffuse, symmetric encephalopathy (Alaskan husky) or encephalomyelopathy (Australian cattle dog, English Springer spaniel) develop within weeks to months. Other signs of neurologic dysfunction in Alaskan huskies with ME include behavioral abnormalities (e.g., anxiety, obtundation, propulsive exploratory behavior), difficulty prehending food, visual deficits, facial hypalgesia, head tremor, hypermetric gait with loss of balance, delayed proprioceptive placing, and varying degrees of tetraparesis. Additional neurologic abnormalities in Australian cattle dogs include progressive spastic tetraparesis with weakness and extensor rigidity of thoracic limbs (sometimes culminating in tetanic contraction), head tilt, and nystagmus. The English Springer spaniel exhibited loss of menace response with some visual deficit, positional vertical nystagmus, and excitement-induced hypermetria and balance loss. The disease tends to be episodic in Alaskan huskies, and slowly progressive in Australian cattle dogs.
- c. Elevated levels of serum and CSF lactate and pyruvate are characteristic features in people with Leigh's syndrome, but have not been documented in dogs with ME. With the exception of one Australian cattle dog with a mild pleocytosis and elevated protein concentration, CSF evaluation has been normal in affected dogs. Advanced imaging (CT, MRI) has been performed in a limited number of dogs. Bilaterally symmetric, cavitary lesions in the brain and/or spinal cord were evident on imaging, which corresponded to lesions discovered at necropsy. Similar to Leigh's syndrome of humans, MRI lesions were hypointense on T1-weighted images, hyperintense on T2-weighted images, and non-contrast enhancing (Fig. 4.8).

Definitive diagnosis of these disorders is based on gross and histopathologic features of the CNS at necropsy. Bilaterally symmetric,

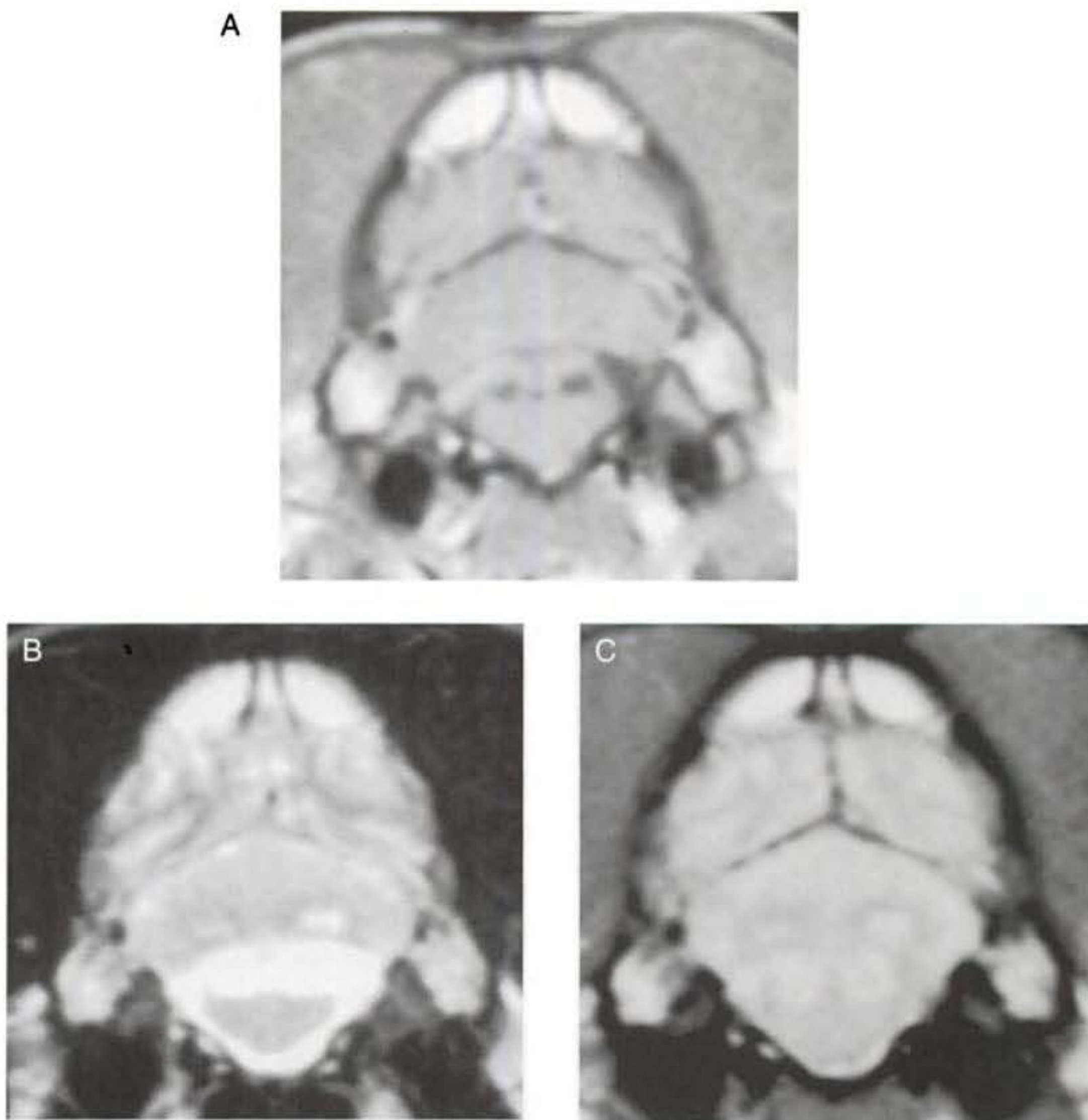


Fig. 4.8. Transaxial brain MR images of a dog with mitochondrial encephalopathy, (A) T1-weighted, and (B) T2-weighted images. Note the symmetric lesions in the brain stem, which are hypointense on T1-weighted images (A) and hyperintense on T2-weighted (B) and intermediate-weighted (C) images (Courtesy of Dr. Ken Harkin; reprinted with permission¹⁰⁶).

spongiform/vacuolar lesions, primarily affecting gray matter, are the pathologic hallmark of these disorders. Histopathologically, multiple areas of the CNS are affected in ME dogs, but some regions are grossly abnormal on gross inspection. Spongiform brain-stem lesions from thalamus to medulla are prominent in Alaskan huskies, the thalamic lesions being

most conspicuous. Australian cattle dogs tend to have cavitory lesions in cerebellar and brain-stem nuclei, as well as in both the cervical and lumbosacral intumescences. The English Springer spaniel had similar lesions in the accessory olivary nuclei of the brain stem. Abnormal mitochondria in neurons and astrocytes have been demonstrated ultrastructurally in several cases of ME.

- d. To date, all cases of ME have been euthanized due to either progression or recurrence of neurologic dysfunction. Most have been euthanized 2–7 mo from the onset of neurologic dysfunction. In people, therapies for mitochondrial encephalopathies are usually ineffective. There has been some small degree of success with dietary management and supplementation (e.g., B vitamins, vitamin E, coenzyme Q, succinate). Such therapy has not yet been described in veterinary ME cases.

D. Neoplastic

1. Primary brain tumors^{107–149}

- a. Primary brain tumors include those neoplasms that originate from brain parenchymal tissue (glial cells and neurons), cells comprising the outer and inner lining of the brain (meninges and ependyma, respectively), as well as vascular elements (e.g., choroid plexus). Primary brain tumors are frequently encountered in dogs and cats and are considerably more common than secondary brain tumors. Meningiomas and gliomas are the most common primary brain tumors in small animals. According to most reports, the most common brain tumor in dogs and cats is meningioma. Multiple histologic subtypes of meningiomas are encountered in dogs. Gliomas (astrocytomas and oligodendrogliomas) are quite common in dogs but are rarely reported in cats. Cats are unlikely to develop primary brain tumors other than meningioma; also, the spectrum of histologic subtypes of feline meningiomas is limited. Choroid plexus tumors are occasionally encountered in dogs. Ependymomas have been described in both dogs and cats but are considered rare. Rarer still in dogs and cats are neuronal tumors, microglial tumors (microgliomatosis), and cerebellar medulloblastomas. Similar to primary brain tumors in people, the causes of these neoplasms are uncertain. Brain tumors exert their pathologic effects both by directly encroaching upon and/or invading brain tissue, and by secondary effects such as peritumoral edema, inflammation, obstructive hydrocephalus, and hemorrhage.
- b. Primary brain tumors can occur in any breed of dog or cat of either sex. Dolichocephalic dog breeds (e.g., German Shepherd dogs, Collies) are more likely to develop meningiomas, whereas brachycephalic breeds (e.g., Boxers, Boston terriers) seem more prone to gliomas. There appears to be a predilection for male cats to develop meningiomas, with no obvious breed predilection for this species. Dogs and cats with brain tumors are

typically middle-aged to older (over 5 yr), with the majority being greater than 9 yr of age. The median age for dogs to develop brain tumors is 9 yr, and for cats it is over 10 yr.

Historical and presenting clinical signs are variable and reflect both the location and the secondary effects (e.g. edema, hemorrhage) of the tumor. Seizures represent the most common presenting clinical sign of neurologic dysfunction in dogs with brain tumors. Cats with brain tumors most commonly present to the veterinarian with a complaint of behavior change. Cats will occasionally have multiple meningiomas, so the clinical signs of dysfunction may reflect more than one intracranial mass lesion. Cerebral tumors are more common than tumors of the brain stem or cerebellum. Cerebral and diencephalic tumors tend to cause clinical signs of dysfunction such as seizure activity, behavior changes, circling, head-pressing, visual deficits, and hemi-inattention syndrome. Proprioceptive placing deficits and neck pain are often appreciable upon neurologic examination. Tumors of the brain stem from midbrain through medulla often cause alterations of consciousness, dysfunction of cranial nerves (other than CN I and CN II), and obvious gait/proprioceptive abnormalities. Cerebellar tumors may result in clinical signs of dysfunction such as ataxia, dysmetria, intention tremors, vestibular abnormalities, and menace reaction deficits with normal vision.

In most cases, clinical signs of neurologic dysfunction occur slowly and insidiously over time, especially with meningiomas. Owners of pets with meningiomas will often retrospectively realize that their pet had a behavior change for months to over a year prior to diagnosis. The subtle behavior changes are often attributed to "old age." However, brain-tumor patients can have subacute to acute development of neurologic dysfunction. These patients may experience sudden exhaustion of brain compensatory mechanisms, or may suffer hemorrhage or acute obstructive hydrocephalus due to the tumor.

- c. The diagnosis of brain tumor should be highly suspected in an elderly dog or cat with slowly progressive signs of brain dysfunction. A brain tumor should also be suspected in animals that experience a recent onset of seizure activity after 5 yr of age, especially in certain breeds (e.g., Golden retriever). Depending upon the location and size of the tumor, such patients may appear neurologically normal interictally.

A definitive diagnosis of a brain tumor cannot be made without a biopsy sample; however, a very confident tentative diagnosis can be made by imaging the brain tumor in a suspect patient. Before pursuing advanced imaging, basic bloodwork (CBC and chemistry profile) and a urinalysis should be performed. Thoracic radiographs should be taken to help rule out the possibility of metastatic cancer. Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used in the

diagnosis of brain tumors. Although specific types of brain tumors can vary in their appearance with these imaging modalities, there are some characteristic features that help distinguish meningiomas from gliomas. Meningiomas tend to have a broad-based, extra-axial attachment (they arise from the periphery of the brain and move inward, or axially), exhibit distinct tumor margins, and uniformly contrast enhance (Fig. 4.9). Meningiomas tend to displace, rather than invade, parenchymal tissue. Some meningiomas will calcify, which can be appreciated on a noncontrast CT image (Fig. 4.10). Gliomas tend to arise from an intra-axial location (from within the substance of the brain, moving outward), often lack distinct tumor margins (they tend to infiltrate, rather than displace normal tissue), and typically contrast enhance poorly and nonuniformly (Fig. 4.11). Choroid plexus tumors and ependymomas tend to be intraventricular in location and often uniformly contrast enhance (Fig. 4.12). The phenomenon of “ring enhancement,” in which a circular ring of contrast enhancement surrounds nonenhancing tissue (Fig. 4.13), is nonspecific, and has been associated with several neoplastic and non-neoplastic brain



Fig. 4.9. Brain MR image (dorsal view, contrast-enhanced) of a dog with a large intracranial meningioma.



Fig. 4.10. Noncontrast transaxial CT image of a meningioma in a cat, with areas of tumoral mineralization.

diseases. However, ring enhancement is often associated with gliomas. These typical imaging features are guidelines only. Meningiomas can arise from the falx cerebri or the choroid plexus, and appear intra-axial. Gliomas can be peripherally located and contrast enhancing. Stereotactic CT-guided biopsy of brain tumors is now available at several veterinary colleges. With this new technology, a definitive diagnosis can be obtained at the time of imaging without the need for major intracranial surgery.

The utility of CSF evaluation for the suspected brain tumor patient is controversial. Cerebrospinal fluid is often abnormal in patients with brain tumors, but the white blood cell (WBC) counts and protein levels are variable and nonspecific for neoplasia. In fact, dogs and cats with meningiomas tend to have CSF with predominantly polymorphonuclear (neutrophilic) WBC counts. The author often does not pursue CSF analysis if the CT or MR image strongly suggests a brain neoplasm. Although the risk of CSF procurement in the face of elevated ICP in a brain-tumor patient is often not great, the potential benefit of a nonspecific CSF result may not outweigh even a small danger of harming the patient with the procedure. Regardless of whether or not CSF analysis is performed, imaging should always precede CSF analysis when a focal neoplasm is highly suspected. Anesthetizing a patient who is most likely to have a brain tumor solely for the purpose of obtaining CSF is generally contraindicated, as the resultant information is unlikely to assist in either planning treatment or estimating prognosis.

- d. Treatment of primary brain tumors is divided into the categories of supportive and definitive. Supportive therapy is aimed at alleviation of the secondary effects of the tumor, whereas definitive therapy is directed toward diminishing tumor volume or eliminating the tumor. Supportive

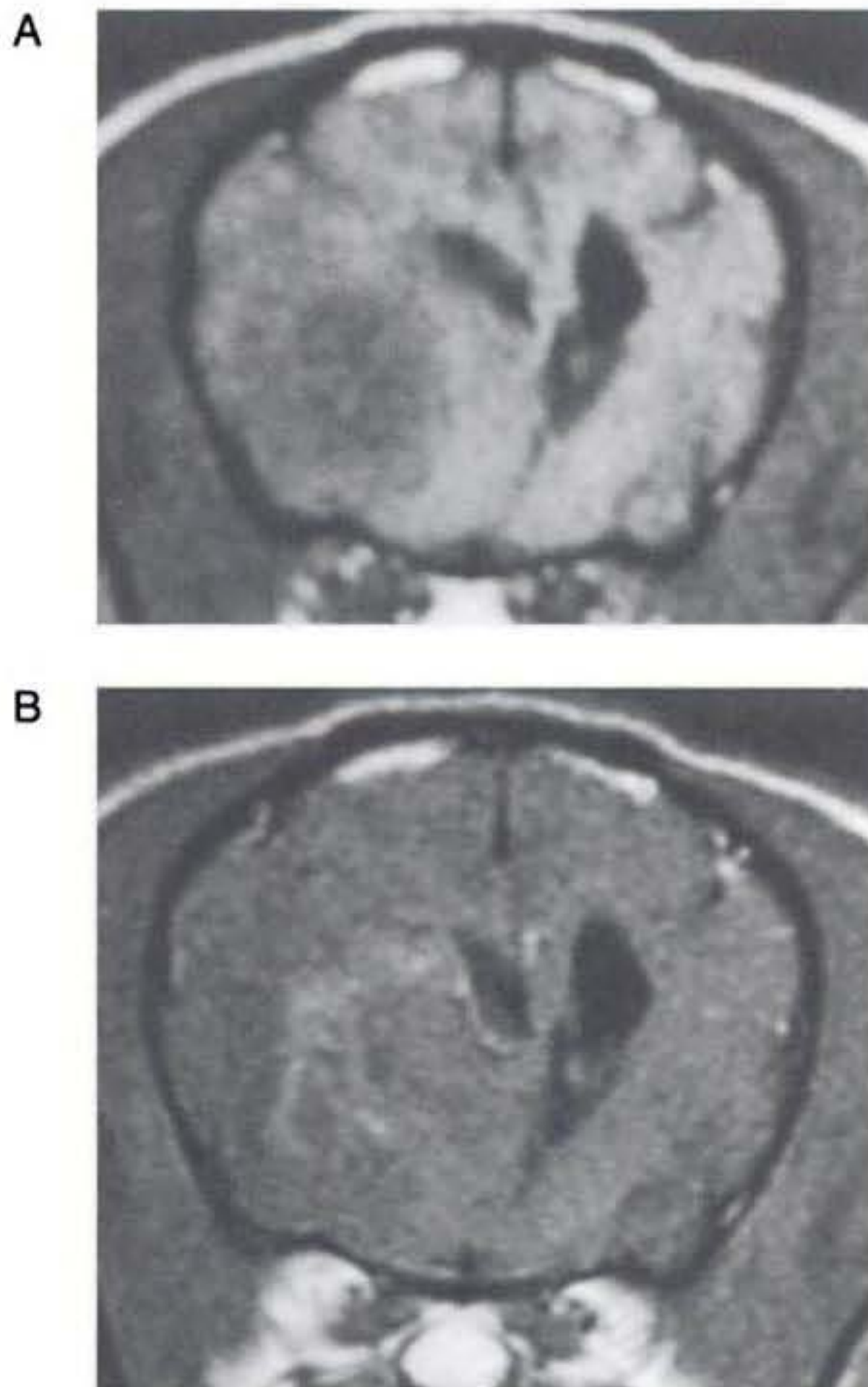


Fig. 4.11. Transaxial MR brain images (T1-weighted) of a dog with an intracranial glioma, before (A) and after (B) contrast administration. Note the patchy contrast enhancement and indistinct tumor margins.

therapy typically consists of an anti-inflammatory dose of oral prednisone (0.5 mg/kg, q 12 hr), that can be increased or decreased, dependent upon patient response. The prednisone should decrease ICP by relieving tumor-associated brain edema and decreasing CSF production. If the tumor results in seizure activity, anticonvulsant drugs (e.g., phenobarbital, potassium bromide) are also prescribed. The author has found that administering standard doses of phenobarbital to dogs with rostral forebrain tumors tends to cause profound sedation. Supportive therapy is usually recommended, whether or not the client opts to pursue definitive therapy for their pet.

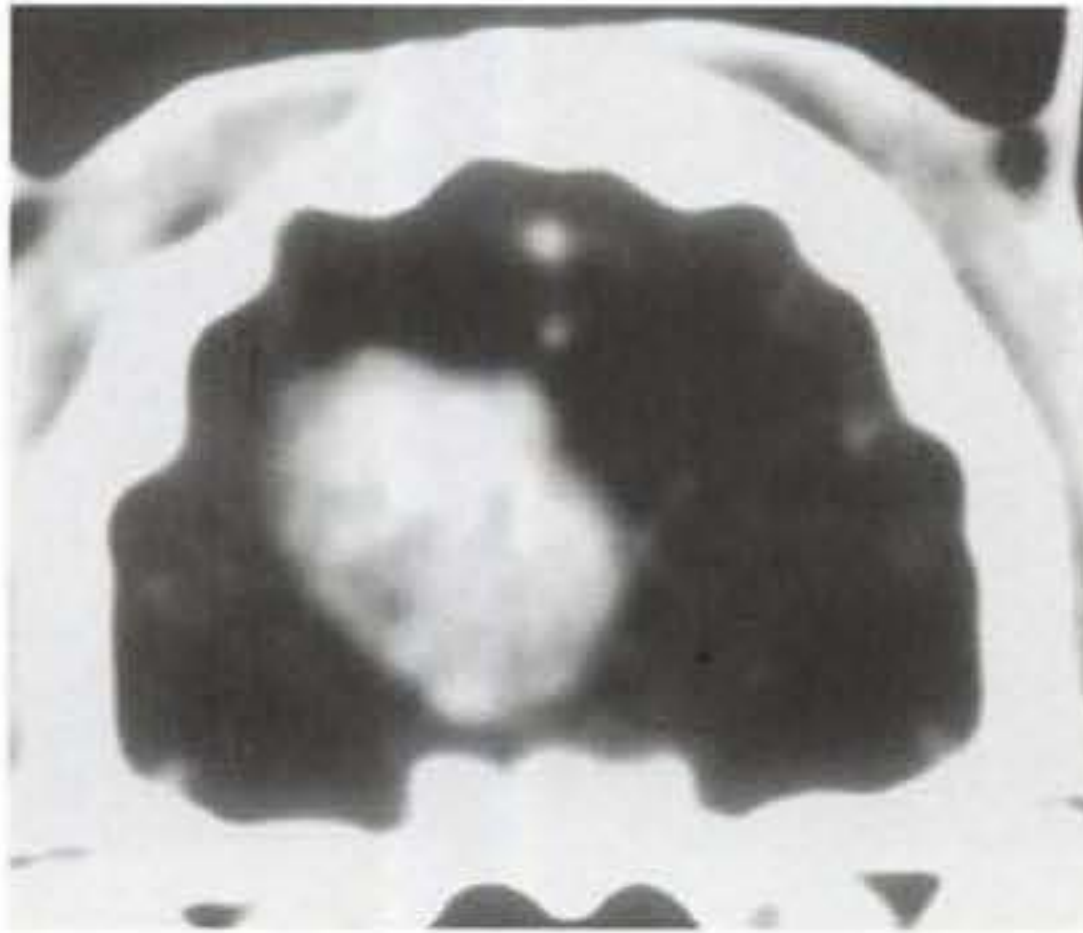


Fig. 4.12. Transaxial contrast-enhanced CT image of a cat's brain, exhibiting an intraventricular ependymoma.

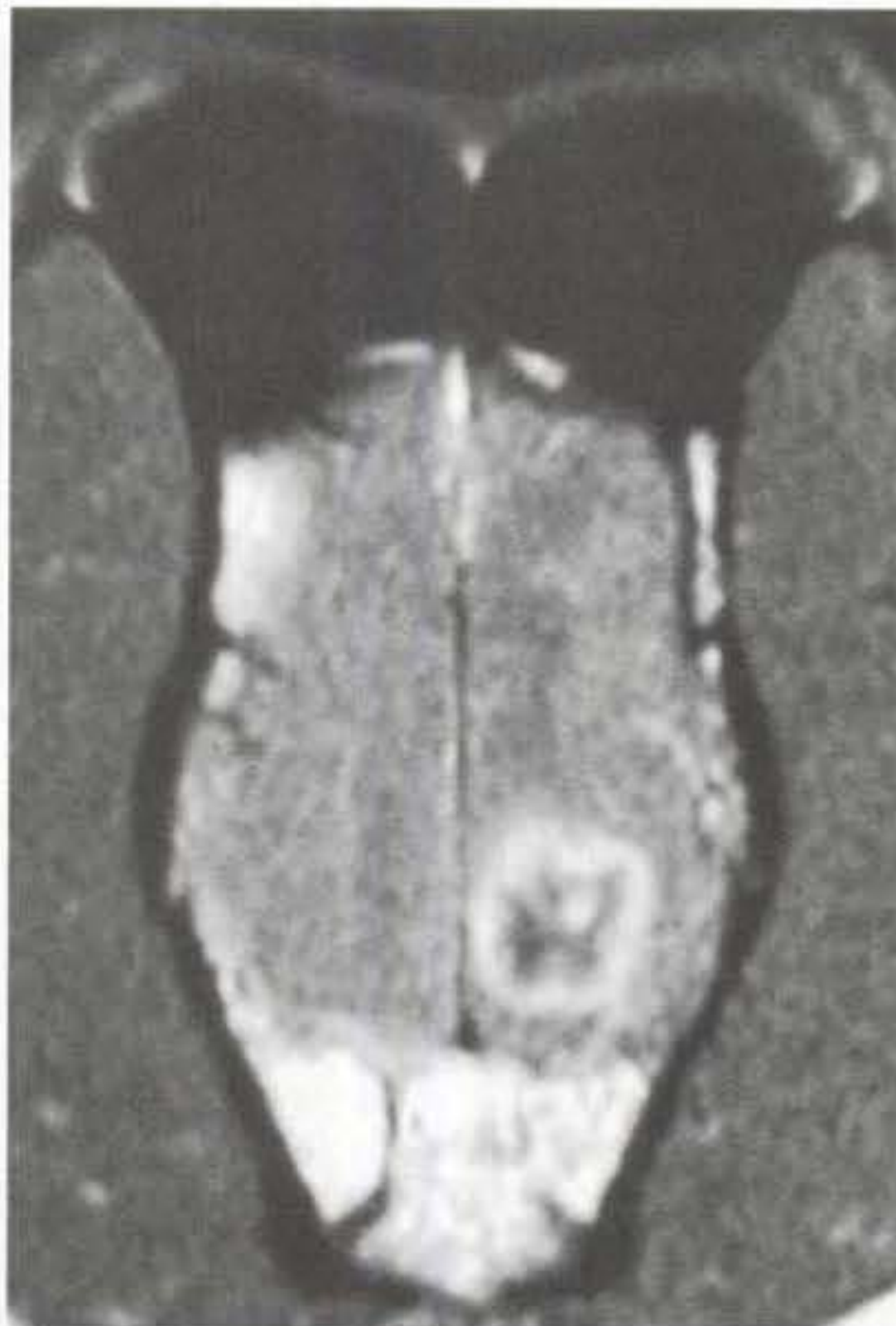


Fig. 4.13. Dorsal MR brain image (T1-weighted, with contrast) of a dog with an intracranial glioma. Note the characteristic "ring enhancement" around the tumor.

There are numerous definitive treatment modalities available for canine and feline brain tumors, but surgical removal/debulking and megavoltage radiation are most commonly used. In addition to removing cancerous tissue, surgical debulking/removal allows for a histologic diagnosis as well as potentially providing an immediate decompressive effect (decreasing ICP). Feline meningiomas are typically located over the cerebral convexities, and tend to “peel away” from normal brain tissue at surgery (Fig. 4.14). In most cases, feline meningiomas can be relatively easily removed *en masse*. Although meningiomas are believed to be radiation sensitive in cats, information concerning radiation therapy for this tumor is lacking, probably due to the success of complete surgical removal. There are no reports describing definitive therapy of feline gliomas. The use of both surgery and radiation therapy have been described in a small number of cats with intracranial ependymoma. Descriptions of definitive therapy for canine brain tumors other than meningiomas and gliomas are largely anecdotal. Canine meningiomas are also often located over the cerebral cortical surface and are surgically accessible. However, meningiomas in the cerebellar and brain-stem regions are frequently encountered in dogs. Cerebellar meningiomas are often surgically accessible; meningiomas in the brain stem may not be accessible. Meningiomas in dogs are much less predictable than those in cats in terms of ease of surgical removal. Unlike cats, there are multiple histologic subtypes of canine meningiomas, and nearly one-third of these tumors are invasive. The author has successfully used intraoperative ultrasound (Fig. 4.15) to assist in locating brain tumors and in judging completeness of removal. Canine meningiomas are generally thought to be



Fig. 4.14. Intraoperative view of a cat's brain following meningioma removal. The tumor was removed *en masse*, leaving an indentation in the cerebrum (Reprinted with permission¹⁰⁷).



Fig. 4.15. Intraoperative ultrasound image of the brain, revealing the presence of an intraparenchymal mass (Reprinted with permission¹⁰⁷).

radiation sensitive. A combination of surgical debulking and radiation therapy is often pursued for canine meningiomas. Surgically inaccessible meningiomas are often treated with radiation therapy alone. Some canine gliomas are surgically accessible, but surgical removal/debulking of gliomas is considerably more difficult than meningiomas. Gliomas tend to infiltrate normal brain parenchyma, and it is often difficult to discern tumor margin from brain tissue at surgery. Although gliomas are not thought to be as radiation sensitive as meningiomas, radiation therapy is often pursued as either a primary or adjunctive therapy for canine gliomas. Typically, external beam megavoltage radiation therapy (using ⁶⁰Co) is administered in fractionated doses (3.3 Gray [Gy] on Monday, Wednesday, and Friday) for 13 treatments (43 Gy total).

Chemotherapy has traditionally been regarded as ineffective for canine and feline brain tumors, mainly due to the poor ability of most drugs to cross the blood-brain barrier (BBB), even when disturbed by the presence of a tumor. However, there are several reports of using nitrosourea compounds such as lomustine (CCNU) and carmustine (BCNU) for canine gliomas. These highly lipid-soluble alkylating agents cross the BBB readily and are used to treat human intracranial gliomas. Oral lomustine (CCNU), at a dosage of 60 mg/m² every 6–8 wk, is recommended for dogs. Since lomustine can cause severe neutropenia, weekly to biweekly CBCs should be checked during treatment, beginning 1 week after drug administration. Broad-spectrum antibiotics are initiated if the neutrophil count drops below 1000 cells/μl. If myelosuppression is

prolonged, administration of granulocyte colony stimulating factor (Neupogen) is recommended. The dose for Neupogen is 5 $\mu\text{g/kg/day}$, subcutaneously for three to five days. The same hepatic microsomal enzymes necessary for generating antineoplastic metabolites from lomustine are also involved in the metabolism of phenobarbital. In order to minimize the possibility of reduced drug efficacy of lomustine, it is recommended that alternatives to phenobarbital be used (e.g., KBr) in seizure patients receiving lomustine therapy.

Chemotherapy and radiation therapy are often applied directly to the tumor in human brain-tumor treatment. Such focal therapy offers the advantage of administering a large dose of treatment to the tumor, while minimizing toxicity to normal tissue. These focal therapies have not been evaluated in dogs and cats. With the recent availability of stereotactic technology, focal therapies for canine and feline brain tumors may be pursued more commonly in the future.

In general, the prognosis for brain-tumor patients treated with supportive therapy alone is poor. The majority of these animals will die or be euthanized due to worsening neurologic dysfunction within 1–4 mo of initial presentation. Other than feline meningioma, prognostic information regarding individual primary brain tumors is highly variable and somewhat conflicting. This is probably due to the lack of controlled studies with large numbers of patients for each of these tumors, as well as the diverse biological behaviors of these tumors compared to feline meningiomas. The prognosis for long-term survival in cats with intracranial meningiomas is typically good to excellent with surgical removal. Median postoperative survival times based upon two recent studies were 21.7 and 27 mo. Tumor recurrence has been estimated to be somewhere between 20% and 25%. Three cats with intracranial ependymoma were treated with radiation therapy, and one of these three also had surgery performed. One of the cats (treated with radiation alone) lived for approximately 4 mo; the other two survived for well over a year. The prognosis for definitive treatment of canine meningiomas is more guarded in comparison with the feline disease. The prognosis for readily resectable meningiomas in dogs is considered fair, but canine meningiomas are not commonly as easily resectable as feline meningiomas. In one report of 4 dogs with intracranial meningiomas, the median postoperative survival time was 4.6 mo. In another report of 14 dogs, the median postoperative survival time was 6.6 mo. In a recent case series, 3 dogs with surgically excised intracranial meningiomas lived an average of 6.7 mo following surgery. A fourth dog was euthanized 2.5 mo after surgery, due to status epilepticus. In one study, radiation therapy for canine meningiomas as a sole therapy resulted in median survival times between 5 and 9 mo. In a more recent report, hypofractionated radiation therapy was associated with median survival

times of 12.5 mo and 10 mo for dogs with extra-axial (probable meningiomas) and intra-axial (probable gliomas) tumors, respectively.

The author has treated several canine meningioma patients with a combination of surgery and radiation therapy, with survival times exceeding 12 mo. In a recent study, the median progression free interval was evaluated for 20 dogs with intracranial meningiomas that had been incompletely resected, then irradiated; the median progression free interval was 30 mo (mean, 35 mo). The limited information concerning definitive therapy of canine meningiomas suggests that combination surgery and radiation therapy may be necessary for prolonged survival in many cases.

Gliomas are associated with a poor prognosis. Data concerning surgical therapy for canine intracranial gliomas are almost nonexistent. Radiation therapy as a sole treatment in 10 dogs with gliomas resulted in a median survival time of approximately 6 mo. Several reports on the use of nitrosourea compounds (carmustine, lomustine) suggest an important role for this form of chemotherapy in the treatment of gliomas; survival times ranging from 7 to 11 mo have been documented. There is no information available concerning the prognosis of other primary canine and feline brain tumors.

2. Secondary brain tumors^{109-115,117,118,127-129,147,150-159}
 - a. Secondary brain tumors include metastatic neoplasia as well as tumors that affect the brain by local extension. Some examples of metastatic neoplasia include mammary, pulmonary, and prostatic carcinoma, hemangiosarcoma, malignant melanoma, and lymphosarcoma. Tumors that may extend into the brain from the periphery include nasal and frontal sinus carcinoma (adenocarcinoma, squamous cell carcinoma), calvarial tumors (e.g., osteosarcoma, chondrosarcoma, multilobular osteochondrosarcoma), pituitary tumors (e.g., pituitary macroadenomas in hyperadrenocorticism), and nerve sheath tumors (e.g., CN V tumors). Similar to primary brain tumors, secondary brain tumors produce clinical signs of neurologic dysfunction both by encroaching upon/invading brain tissue and by secondary effects such as hemorrhage, inflammation, and obstructive hydrocephalus.
 - b. As with primary brain tumors, secondary brain tumors are primarily encountered in middle-aged to older dogs (usually) and cats. Medium-sized to large-breed dolichocephalic dogs are prone to developing nasal/frontal sinus carcinomas and calvarial tumors, whereas small and brachycephalic breeds of dogs are more likely to develop pituitary macroadenomas. Clinical signs of neurologic dysfunction reflect tumor location(s) within the brain as well as the degree of secondary effects of the tumor(s). Unlike primary brain tumors, secondary brain tumors are often associated with rapid development of neurologic dysfunction. Patients with metastatic disease may exhibit clinical signs of extraneural

organ dysfunction due to neoplasia (e.g., collapse due to hemorrhage from a splenic hemangiosarcoma). Dogs with nasal carcinomas often, but not always, have historical/clinical evidence of epistaxis. Obvious skull deformities may be appreciable with nasal/frontal carcinomas and calvarial tumors. Most dogs with pituitary macroadenomas large enough to cause neurologic dysfunction display clinical signs of hyperadrenocorticism (e.g., PU/PD, polyphagia, pot-bellied appearance).

- c. Similar to primary brain tumors, definitive diagnosis of secondary brain tumors depends upon histopathologic identification of the specific brain tumor. As with primary brain tumors, stereotactic biopsy may be potentially helpful in diagnosing some secondary brain tumors. In the case of metastatic neoplasia, identifying an extraneural neoplasia (e.g., pulmonary mass) in a patient with signs of encephalopathy is strong evidence for a secondary brain tumor. It must be kept in mind, however, that older animals may develop two or more primary tumors concurrently. A solitary pulmonary mass in a dog exhibiting signs of focal forebrain dysfunction does not necessarily equate to metastatic disease. Although rare, intracranial meningiomas have also been reported to metastasize to the lungs. The appearance of multiple intracranial masses on CT or MR imaging in a patient suspected of having metastatic disease is also strong confirmatory evidence for secondary brain neoplasia (Fig. 4.16). Metastatic carcinomas can, on occasion, appear as solitary, well-circumscribed, brain tumors.

Nasal/frontal sinus carcinomas tend to cause bony destruction, which is readily visible on either anesthetized skull films or CT/MR images (Fig. 4.17). Similarly, calvarial tumors are often readily visualized with radiographs or CT/MR imaging (Fig. 4.18). CT imaging is often preferred for the diagnosis of these neoplasms, as the brain as well as bony structures are visualized. In nasal/frontal sinus carcinomas, CT or MRI can provide confirmatory evidence of invasion into the cranial cavity (Fig. 4.19). Imaging a calvarial osteosarcoma, chondrosarcoma, or multilobular osteochondrosarcoma with CT can be invaluable in both diagnosis and treatment planning.

In addition to typical historical and clinical features of hyperadrenocorticism, diagnosis of pituitary macroadenomas is based upon results of endocrine testing (e.g., ACTH stimulation, dexamethasone suppression tests) and identifying a mass in the region of the pituitary on a CT (Fig. 4.20) or MR image.

Tentative diagnosis of a CN V-associated nerve sheath tumor invading the calvarium is based upon typical clinical signs of CN V dysfunction, clinical evidence of brain-stem involvement, and visualizing an intracranial mass on CT or MR imaging.

- d. Supportive treatment of secondary brain tumors in dogs and cats is identical to that for primary brain tumors. Also, as with primary brain tumors,

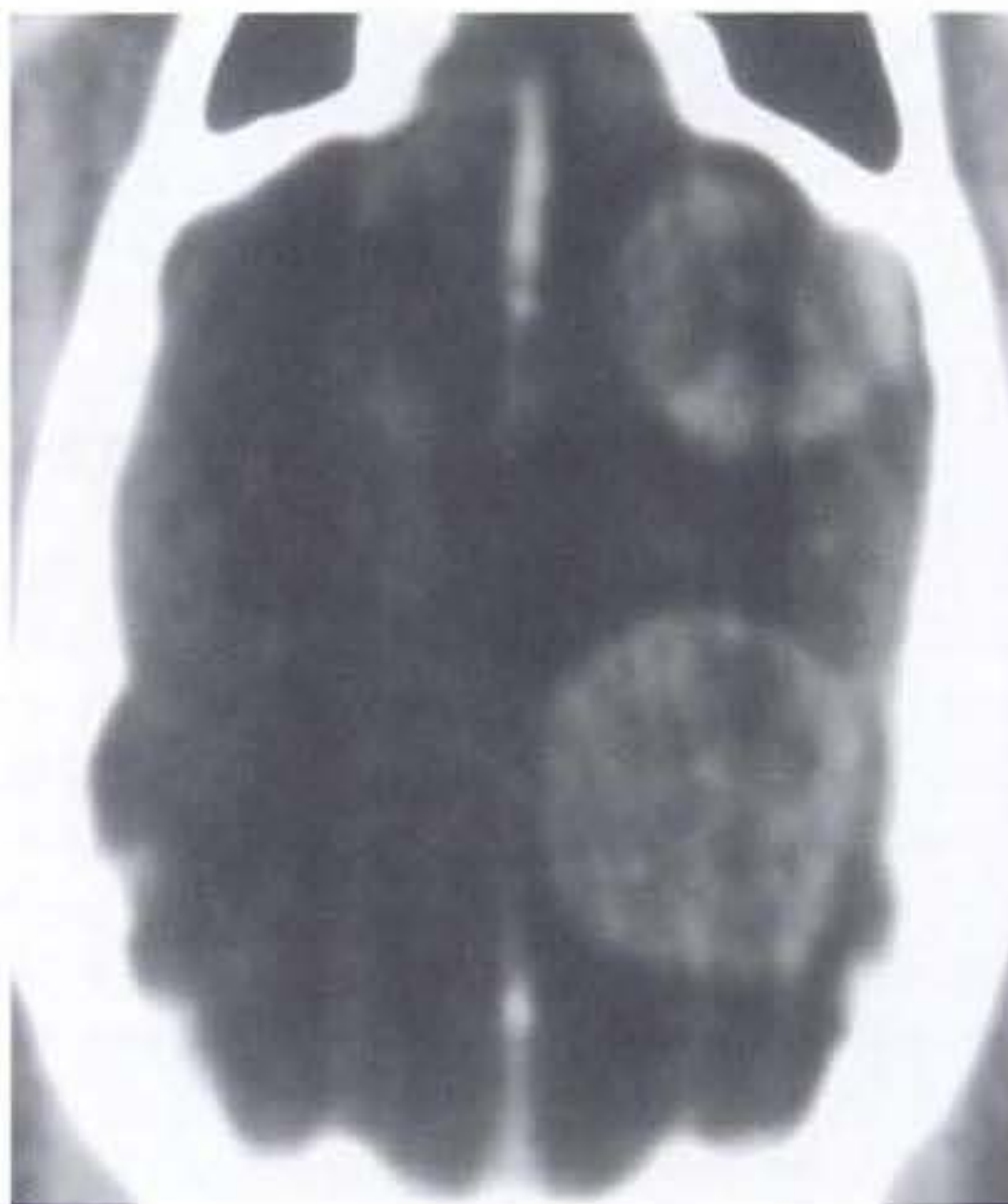


Fig. 4.16. Dorsal CT brain image of a dog with several metastatic brain tumors.

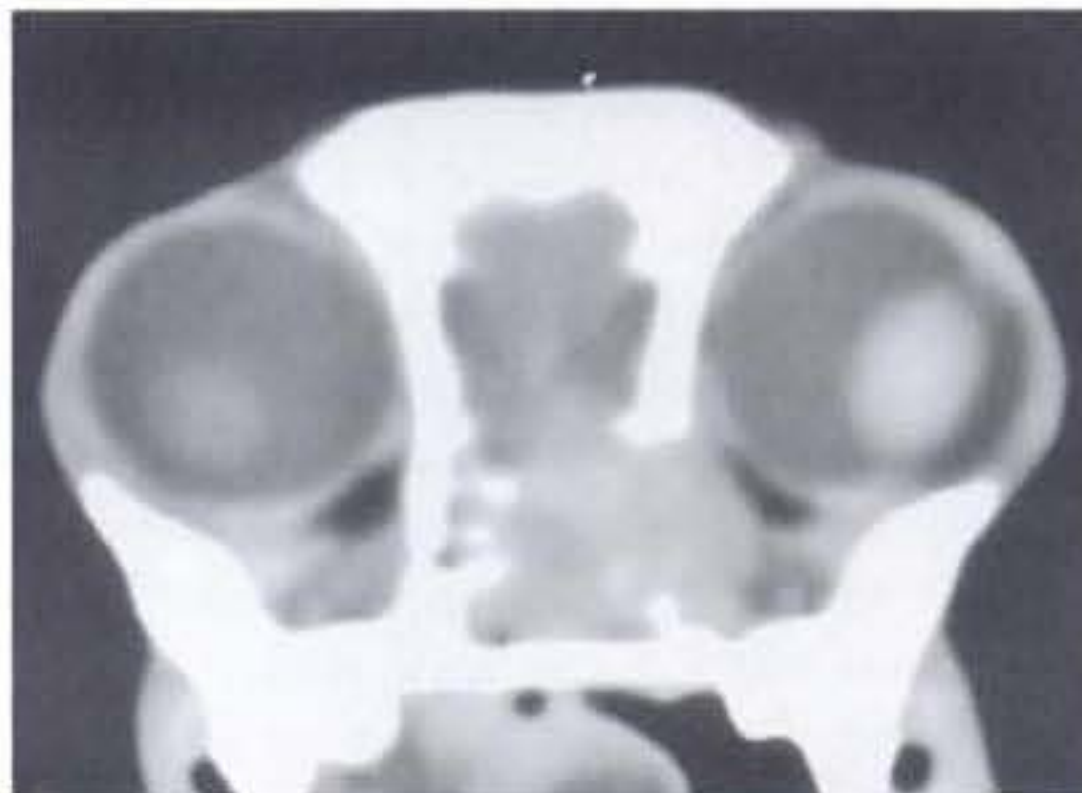


Fig. 4.17. Transaxial, contrast-enhanced CT image of a dog with a nasal sinus carcinoma. Note the bony lysis associated with the tumor and invasion of the mass into the cranial vault (Courtesy of Dr. Mike Walker).

surgery and radiation therapy are the main definitive treatment modalities available for secondary brain tumors. Definitive treatment of metastatic secondary brain tumors is rarely attempted, due to the poor prognosis associated with these tumors, even in the absence of brain involvement. In some cases of single metastases (e.g., pulmonary carcinoma), definitive treatment of both the primary and secondary neoplasms may be indicated.

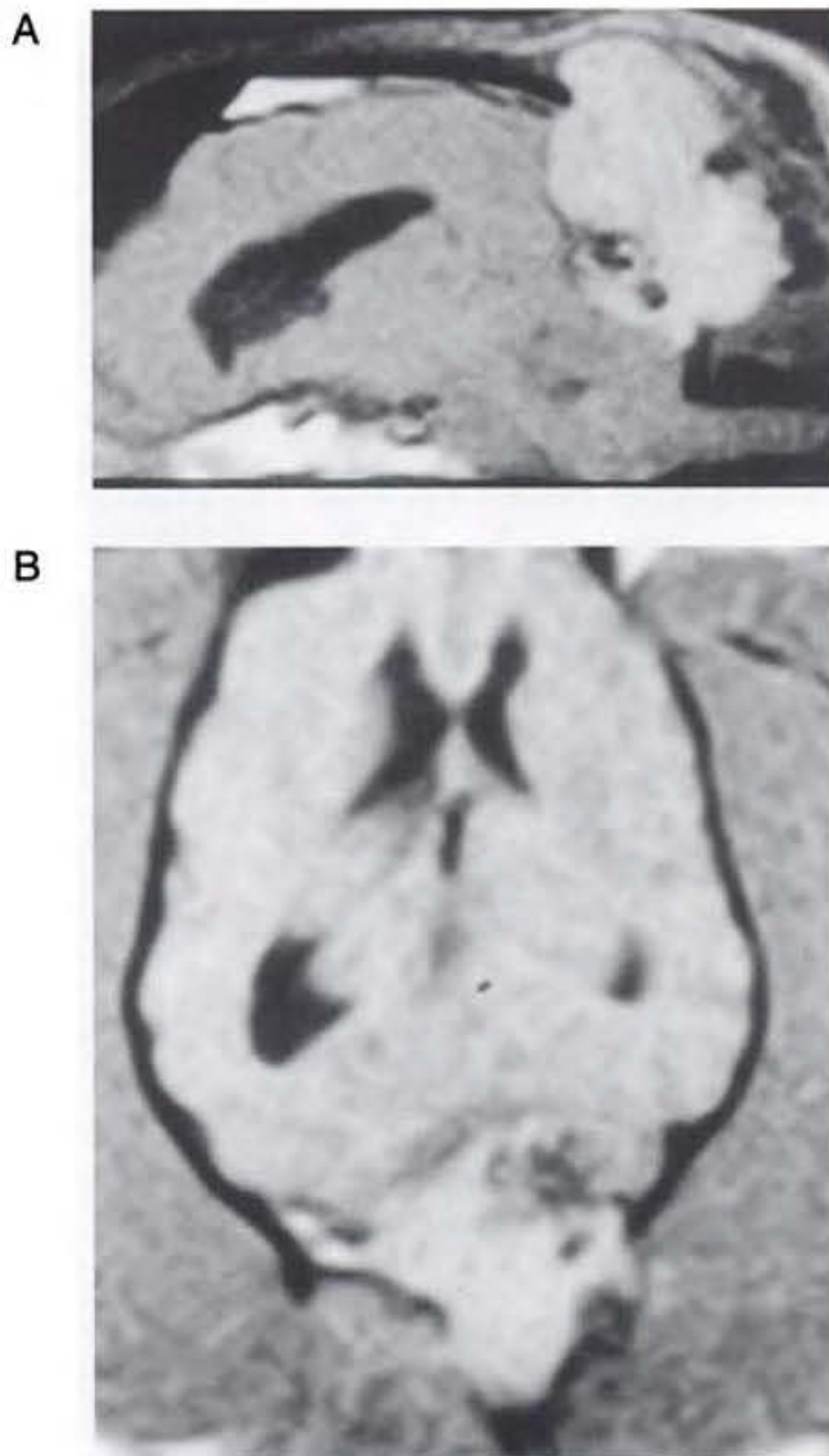


Fig. 4.18. Sagittal (A) and dorsal (B) MR brain images (T1-weighted, with contrast) of a dog with a multilobular osteochondrosarcoma of the calvarium causing cerebellar compression.

Nasal/frontal carcinomas with invasion into the cranial cavity are also rarely treated, as the prognosis for even short-term control of neurologic dysfunction is considered poor. Patients with calvarial tumors (e.g., multilobular osteochondrosarcoma), if aggressively treated with surgical resection, are likely to have prolonged survival times. These neoplasms are slow to recur and metastasize. In a recent report, the median survival time for multilobular osteochondrosarcoma of the skull was approximately 26 mo.

Pituitary adenomas are felt to be radiation sensitive, and median survival times after megavoltage irradiation are reported to be approximately



Fig. 4.19. Dorsal CT brain image of a dog with a nasal frontal sinus carcinoma invading through the cribriform plate.

1–2 yr. Although traditionally rarely pursued due to technical complexity, excellent results of hypophysectomy via a transphenoidal surgical approach have recently been documented in dogs with pituitary-dependent hyperadrenocorticism.

In a recent report of trigeminal (CN V) nerve sheath tumors in dogs, the median survival time of nontreated cases was 12 mo. Two dogs treated with surgery were alive at the time of manuscript submission, 5 and 27 mo after surgery. One of the dogs that underwent surgery was euthanized due to progressive neurologic dysfunction 5 mo postoperatively.

E. Nutritional

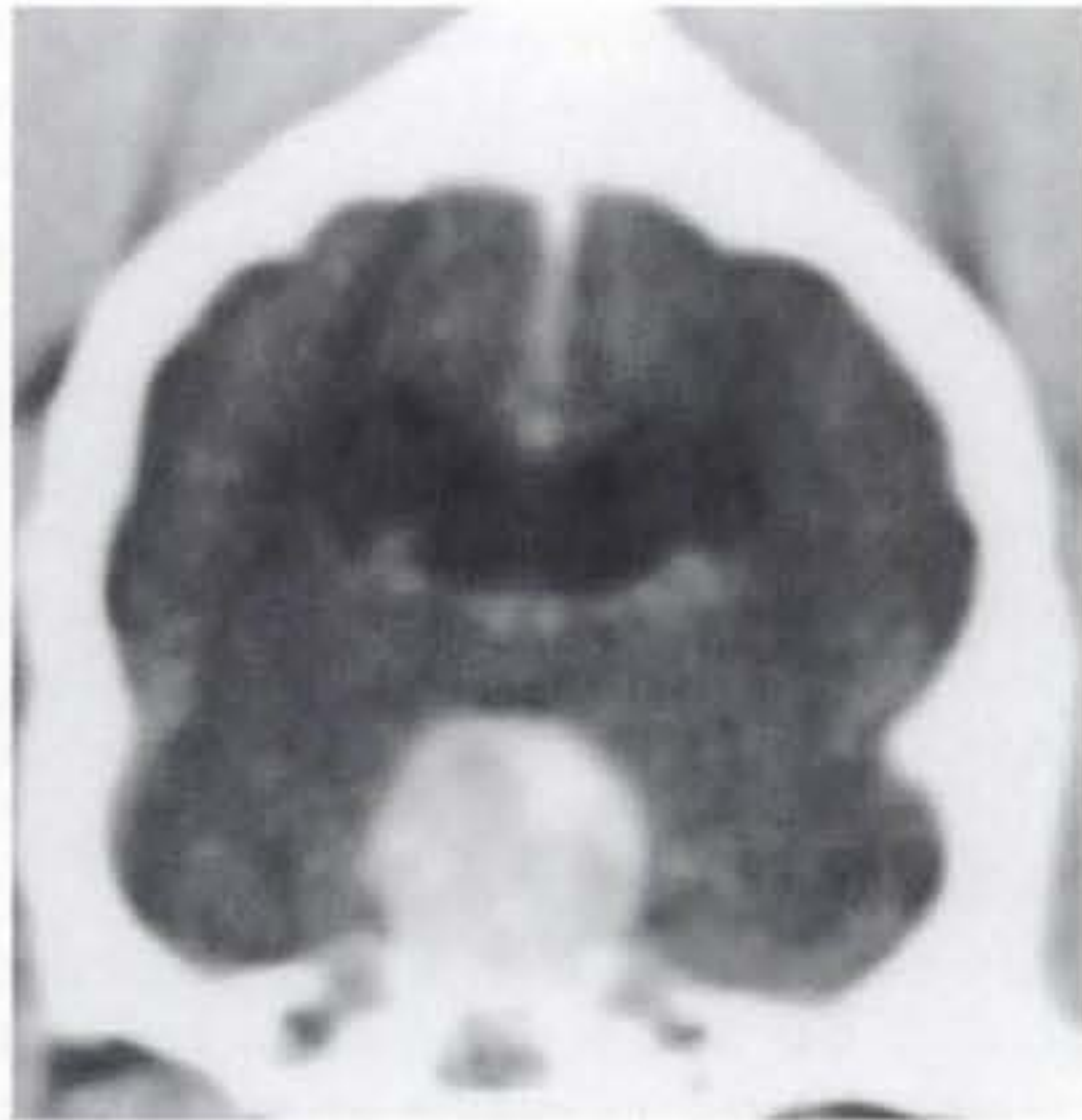


Fig. 4.20. Transaxial contrast-enhanced CT brain image of a dog with a pituitary macroadenoma.

1. Thiamine deficiency^{2,61,62}
 - a. Thiamine deficiency is rarely a clinical problem in dogs and cats. Thiamine must be provided in the diet, as dogs and cats are unable to produce it endogenously. Thiamine (vitamin B₁) is a necessary cofactor for normal carbohydrate oxidation, and its deficiency results in insufficient ATP production in the brain with subsequent neuronal dysfunction and death (if not treated). Fish is high in thiaminase, and feeding an all-fish diet to cats can lead to thiamine deficiency. Overcooking canned food or meat, causing heat destruction of thiamine, has led to thiamine deficiency in dogs. Finally, feeding meat preserved with sulfur dioxide to dogs and cats may result in thiamine deficiency.
 - b. Neurologic dysfunction due to thiamine deficiency tends to be acute and rapidly progressive. In both dogs and cats, signs of neurologic dysfunction due to thiamine deficiency typically include vestibular ataxia, decreased mentation (obtundation leading to coma, if not treated), ventroflexion of the head and neck, seizure activity, pupillary dilation with absent menace responses, and head tremors. Left untreated, affected animals progress to a comatose state with opisthotonus (decerebrate posture) and ultimately death.
 - c. Antemortem diagnosis of thiamine deficiency is typically based upon characteristic clinical signs of thiamine deficiency in a dog or cat receiving a thiamine-deficient diet. A positive response to thiamine administration also supports the diagnosis. Elevated blood pyruvate and lactate levels, and

decreased erythrocyte transketolase activity are supportive of the diagnosis, but these tests are rarely done. In animals that die due to thiamine deficiency, characteristic bilaterally symmetric lesions (petechial hemorrhages) are appreciable throughout the brain at necropsy, especially in the caudal colliculi of the midbrain.

- d. Treatment of suspected thiamine deficiency is thiamine hydrochloride via the intravenous, intramuscular, or subcutaneous route. The dosage for dogs is 5–50 mg/day, and for cats, 1–20 mg/day. If recognized and treated early, the prognosis for survival of thiamine deficiency is good. If not treated rapidly in the early period of neurologic dysfunction, the prognosis for survival is guarded to poor.

F. Inflammatory/infectious

A wide variety of inflammatory brain conditions affects dogs and cats. For some of these conditions, an infectious agent is identifiable. For others, no infectious agent has been found. Some of the inflammatory brain diseases may have an autoimmune etiology. Diagnosis and treatment of inflammatory brain disorders can be frustrating. The “classical” description of a dog or cat with an inflammatory/infectious brain disease is a patient with a multifocal/diffuse encephalopathy, often with severe cervical spinal hyperesthesia. With infectious etiologies especially, fever and abnormal CBC results are often expected. In many cases, the affected patient will not follow the “classical” description of an inflammatory/infectious encephalopathy.

Historical, clinical, and laboratory data are typically combined in an effort to arrive at an antemortem diagnosis and institute appropriate therapy. Cerebrospinal fluid results may be particularly helpful when diagnosing diseases in this category. In a recent report, a specific diagnosis was not ascribable to at least one-third of canine infectious/inflammatory disorders of the central nervous system (CNS).¹⁶⁰ In the majority of canine and feline inflammatory brain diseases, especially those of confirmed infectious etiology, the prognosis for survival is poor. Prognostic data for many of these diseases are based mainly upon case reports and publications that focus on the pathologic aspects of the specific diseases. Considering the wide variety of potential clinical presentations for inflammatory/infectious brain disorders, and the frequent requirement of timely and aggressive treatment for successful outcomes, the clinician should maintain a high index of suspicion for these diseases. The pathophysiology of infectious meningoencephalitis is complex and is briefly reviewed below under bacterial meningoencephalitis. There are numerous treatment regimens for the various infectious agents discussed below, and this text is meant to provide an overview of these treatment options. The suggested references should be consulted for more detailed information.

1. Bacterial meningoencephalitis^{160–170}

- a. In general, bacterial infections of the nervous system are felt to be uncommon. It is not clear whether these infections are truly rare or are rarely

reported due to high early mortality. Bacteria can gain access to the brain via the hematogenous route or by extension of infection from a neighboring focus (e.g., extension of otitis interna into the brain stem). The blood-brain barrier (BBB) and absence of a lymphatic system in the CNS help protect it from microbial invasion. Once the BBB has been successfully breached by an infectious agent, the immunologically privileged nature of the CNS represents an advantage to the invading organism and a detriment to the host. The CNS is poorly endowed with immunologically active cells and complement, which provides a favorable environment for bacterial growth. Once cells from the systemic immune system are recruited into the CNS, the infection is often well established.

Bacterial infections of the brain may result in neurologic dysfunction by producing a mass effect (i.e., organized abscess) or release of bacterial toxins. However, the main cause of neurologic deficits is the secondary inflammatory response induced by the bacteria. Inflammatory mediators, such as interferons, tumor necrosis factor (TNF), prostaglandins, and kinins are produced by white blood cells (WBCs) in response to bacteria. These mediators result in edema, vasculitis, and infarction. By attracting additional WBCs to the infection focus or foci (chemotaxis), a self-perpetuation of tissue damage ensues. The most commonly implicated organisms in canine and feline bacterial meningoencephalitis have been *Staphylococcus* and *Streptococcus* species, *Pasteurella multocida* (especially cats), *Actinomyces* and *Nocardia* species, as well as anaerobes (e.g., *Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, *Eubacterium*). In a recent report of canine bacterial meningoencephalitis, the most common causative organisms were *Escherichia coli*, *Streptococcus* species, and *Klebsiella* species. Gram-negative infections were most common, and single versus multiple organism infections were equally likely.

- b. Dogs and cats of any age, breed, or sex may develop bacterial meningoencephalitis, but it is more common in young to middle-aged animals (e.g., 1–7 yr). In a recent study, most of the affected dogs were purebred, with a median age of 5 yr at presentation. Clinical signs of neurologic dysfunction are often acute and rapidly progressive. Fever and cervical hyperesthesia are considered classical features of bacterial meningoencephalitis, but may not be evident. Fever and cervical hyperesthesia have been reported to occur in approximately 40% and 20% of canine bacterial meningoencephalitis cases, respectively. As with other diseases, clinical signs of neurologic dysfunction depend upon the location(s) and extent of the lesion(s). Both focal and multifocal encephalopathy are possible, involving the forebrain and/or brain stem. Some patients may appear generally ill due to systemic bacterial disease.
- c. A tentative diagnosis of bacterial meningoencephalitis is based upon historical and clinical data, as well as results of laboratory tests. A positive response to antibiotic drugs also supports the diagnosis. CBC results may

indicate a systemic inflammatory response, but this is often not the case. Abnormalities such as leukocytosis, leukopenia, and thrombocytopenia have been reported to occur in approximately 57% of canine bacterial meningoencephalitis cases. Abnormalities on serum chemistry profiles (e.g., elevated ALT and SAP levels, hypoglycemia, hyperglycemia) are apparent in over 70% of such cases. Advanced imaging (CT, MRI) may be helpful in diagnosing mass lesions (Fig. 4.21) or obstructive hydrocephalus. The most valuable information is obtained from CSF analysis, which is abnormal in over 90% of cases. With acute bacterial meningoencephalitis, a suppurative CSF pattern, often with degenerate and toxic-appearing neutrophils, is typical. Protein levels are also often elevated. The presence of intracellular bacteria in the CSF sample confirms the diagnosis. Extracellular bacteria may represent causative agents but may also be contaminants. Positive CSF, blood, and/or urine culture results also support the diagnosis of bacterial meningoencephalitis. Since these culture results are often negative (approximately 80%) in confirmed bacterial meningoencephalitis cases, a negative result should not be overinterpreted.

d. Ideally, antibiotic treatment of bacterial meningoencephalitis is based upon culture/sensitivity results of the causative organism. As this is often not obtainable, antibiotic therapy is often based on gram-stain results of

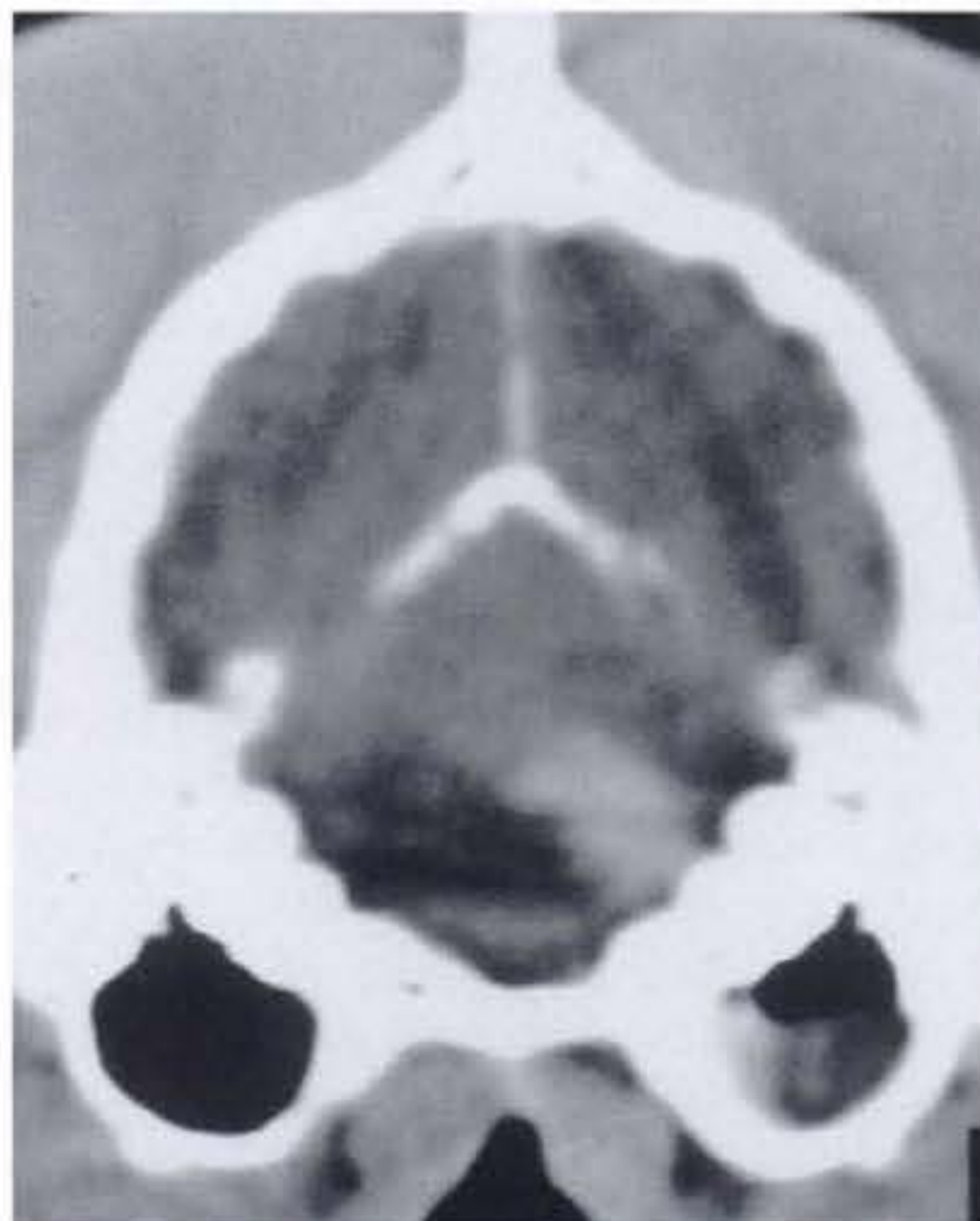


Fig. 4.21. Transaxial contrast-enhanced CT brain image of a dog with otitis media/interna extending into the brain stem (Reprinted with permission¹⁶⁵).

organisms seen on CSF analysis, or on the most likely pathogen(s), if organisms are not seen. Appropriate antibiotics for bacterial meningoencephalitis should ideally be bactericidal, have a low-level protein binding, and be able to cross the BBB. Intravenous therapy is recommended for at least the initial three to five days of therapy. High intravenous doses of ampicillin (e.g., 22 mg/kg, q 6 hr) has been recommended as an appropriate therapeutic choice for most cases of canine and feline bacterial meningoencephalitis. Ampicillin crosses the inflamed BBB relatively well, and is bactericidal. If a gram-negative infection is suspected or confirmed, enrofloxacin (e.g., 10 mg/kg IV, q 12hr) or a third-generation cephalosporin (e.g., cefotaxime at 25–50 mg/kg IV q 8 hr) are good choices. Metronidazole (10 mg/kg IV **slowly**, q 8 hr) is an excellent antibiotic choice for most anaerobic infections. Intravenous metronidazole should be administered over 30–40 min, as rapid infusion can lead to hypotension. In severe cases of bacterial meningoencephalitis, it may be prudent to institute combination antimicrobial therapy while awaiting CSF laboratory results (gram stain, culture results). Based on recent information concerning causative agents in canine bacterial meningoencephalitis, inclusion of antibiotics with strong activity against gram-negative bacteria is highly recommended. Although chloramphenicol is broad spectrum and readily crosses the BBB, its use in human and experimental canine bacterial meningitis has been associated with a high relapse rate, presumably due to the bacteriostatic nature of this drug. Once a positive response to intravenous antibiotic therapy is achieved, the patient can be switched to oral therapy. Trimethoprim-sulfonamide (15 mg/kg PO, q 12 hr) is broad and bactericidal, and it readily penetrates the BBB, even when the BBB is not inflamed. Oral formulations of enrofloxacin and metronidazole are also available. Recommendations for the length of oral antibiotic therapy vary. Discontinuation of antibiotic therapy is ideally based both on clinical signs as well as normal follow-up CSF tap results. However, the latter-mentioned information is often not available. In general, antibiotic therapy should be administered for 10–14 days after resolution of clinical signs of disease.

Although glucocorticoid use in the face of infection is usually contraindicated, there is abundant evidence that transient (maximum of 4 days), anti-inflammatory doses (e.g., 0.15 mg/kg dexamethasone, IV, q 6 hr) of glucocorticoids improve outcomes in people with bacterial meningitis. Such therapy should be considered for dogs and cats with this disorder. If CT or MR imaging localizes a surgically accessible abscess, surgical intervention may play an important role in the management of bacterial meningoencephalitis.

Unfortunately, there are no reports describing large groups of dogs or cats treated appropriately for confirmed bacterial meningoencephalitis.

The sparse information available suggests a poor prognosis overall. However, survival rates in people appropriately treated for bacterial meningitis are over 70%. There are isolated reports of successful outcomes in cases of canine and feline bacterial meningoencephalitis. Similar to human bacterial CNS infections, the key to successful therapy of dogs and cats with bacterial meningoencephalitis is early diagnosis and rapid, aggressive therapy.

2. Fungal meningoencephalitis^{160,161,171–183}

- a. There is a wide variety of fungal organisms that may invade the CNS, including *Cryptococcus*, *Coccidioides*, *Blastomyces*, *Histoplasma*, *Aspergillus*, and the phaeohyphomycoses (e.g., *Cladosporium*). *Cryptococcus neoformans* is by far the most common fungal organism associated with meningoencephalitis in dogs and cats, and there is very little clinical information available pertaining to meningoencephalitis caused by other fungal organisms. Fungal disease is contracted by dogs and cats via inhalation of fungal spores. Infection of the CNS can occur via local extension (e.g., nasal/frontal sinus) or hematogenously.

Similar to bacterial CNS infection, clinical signs of neurologic dysfunction may be due to a mass effect (e.g., gelatinous mass of fungal organisms, fungal granuloma), or to a more disseminated inflammatory response to the invading organisms. In people with fungal CNS infections, an underlying state of immunosuppression is usually present. While this may also be the case in some canine and feline CNS fungal infections, an underlying immunodeficiency state is often not identified in dogs and cats with fungal meningoencephalitis.

- b. As with bacterial meningoencephalitis, dogs and cats with fungal meningoencephalitis are typically young to middle-aged (e.g., 1–7 yr). American Cocker spaniels and Siamese cats appear to be predisposed to developing CNS cryptococcosis. Although clinical signs of neurologic dysfunction may be acute in onset and rapidly progressive, fungal meningoencephalitis is often characterized by slow progression (weeks to months) of neurologic dysfunction, often preceded by a period of nonspecific illness (e.g., lethargy, anorexia). Focal and multifocal encephalopathy are possible, affecting the forebrain and/or brain stem. Clinical evidence of extraneural fungal infection is common in cases of fungal meningoencephalitis. With cryptococcosis, extraneural infection around the head region (eyes, nasal and frontal sinuses) is most likely.
- c. The diagnosis of fungal meningoencephalitis is based upon identifying the presence of a fungal organism in a patient displaying signs of encephalopathy. Finding a fungal organism in an extraneural site in a patient with brain dysfunction is strong evidence for fungal meningoencephalitis. Identifying the organism in a CSF sample is the strongest evidence to support the diagnosis, and this is more likely to occur with *Cryptococcus* infections (93% in dogs) than with other fungal infections.

Special stains are available to help identify specific fungi on cytology specimens. CNS fungal infections typically cause a mixed-cell pleocytosis with elevation of protein on CSF examination. The nature of the pleocytosis is highly variable, but usually includes a large proportion of both mononuclear cells as well as neutrophils, typical of a granulomatous disease.

Eosinophils may also comprise a large proportion of CSF WBCs in fungal meningoencephalitis patients. Testing of CSF and/or serum for antibodies to fungal antigens can also be performed. These tests are very reliable for *Cryptococcus*, *Coccidioides*, and *Blastomyces* infections, less so for *Aspergillus* infections, and unreliable for *Histoplasma* infections. No such tests are available for the phaeohyphomycoses. The various fungi can also be cultured from bodily fluids, using special growth media; this can be hazardous to human health in the case of coccidioidomycosis and histoplasmosis.

Bloodwork abnormalities are variable and nonspecific. Nonregenerative low-grade anemia, neutrophilia, and hypercalcemia (due to granulomatous disease) are examples of such abnormalities. Fungal elements may be identifiable in urine samples. Ophthalmic examination may reveal evidence of inflammatory disease (e.g., uveitis, chorioretinitis). Pulmonary lesions may be identifiable in some cases (e.g., *Histoplasma*, *Blastomyces*, *Coccidioides*) on thoracic radiographs. Cats with suspected or confirmed fungal meningoencephalitis should be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). Advanced imaging (CT, MRI) may be helpful in some cases of fungal meningoencephalitis that have solitary mass lesions (e.g., granulomas) and/or obstructive hydrocephalus.

- d. The treatment and prognosis for canine and feline fungal meningoencephalitis are poorly defined. Similar to bacterial meningoencephalitis, data describing large numbers of dogs and cats with CNS fungal disease treated with appropriate antifungal agents are lacking. Meningoencephalitis caused by *Aspergillus* or phaeohyphomycosis species is likely to be fatal. Few antifungal drugs are able to cross the BBB effectively, even when inflamed. However, flucytosine (5-fluorocytosine) and the relatively new triazole drug fluconazole are two antifungal drugs that readily cross the BBB. There are several reports of sustained remissions or cures in CNS cryptococcosis patients treated with drug combinations that included flucytosine and/or the newer triazole drugs (itraconazole and fluconazole). Flucytosine use alone may lead to the development of drug resistance. The author successfully treated a dog with coccidioidomycosis of the brain stem using fluconazole. Once clinical signs of disease are controlled, most patients with fungal meningoencephalitis will require long-term antifungal therapy (months). The decision of when to discontinue antifungal therapy should be based upon clinical signs, repeat CSF results, and CSF/serum

titers for the organism (if appropriate). Since fluconazole penetrates the BBB well and itraconazole does not, fluconazole for CNS fungal infection is the preferred antifungal agent (5 mg/kg PO, q 12 hr for 2–3 mo). The main drawback of fluconazole use is the high cost of the drug.

3. Viral meningoencephalitis^{160,161,183–209}

- a. The most frequently encountered viral infections of the brain in dogs and cats in clinical practice are canine distemper (paramyxovirus) virus and feline infectious peritonitis (FIP-coronavirus) virus, respectively. Other, less-common causes of viral meningoencephalitis include rabies virus (dogs and cats), feline immunodeficiency virus (FIV, a lentivirus), canine herpesvirus, feline parvovirus (panleukopenia virus), feline Born disease virus (BDV), and pseudorabies (dogs and cats, caused by a porcine herpesvirus). CNS involvement is rarely reported in association with canine adenovirus (infectious canine hepatitis virus), canine parainfluenza virus (also a paramyxovirus), and canine parvovirus. Meningoencephalitis associated with these latter three canine viruses will not be discussed in this text.

Canine herpesvirus infection typically affects neonatal puppies less than 3 wk of age and is associated with a high mortality rate due to severe systemic illness. Surviving dogs may have retinal and cerebellar dysplasia. There are multiple routes of viral infection, but inhalation is most common. Rabies is typically contracted via bite wounds from infected animals, and pseudorabies from ingestion of infected raw pork meat. FIV may also be spread via bite wounds. There are a number of reports of suspected vaccine-induced canine distemper CNS infections. Feline Born disease may be transmitted by saliva or nasal secretions; ingesting rodents that carry the virus may also be a route of infection. Viruses can damage brain parenchyma via both direct (e.g., cytolytic) and indirect (e.g., immune-mediated) effects. Some viruses have a predilection for neuronal and glial cells, and are termed “neurotropic.” Such viruses include the causative agents of canine distemper, rabies, pseudorabies, and feline Born disease.

- b. As with other CNS infectious diseases, affected animals are often young to middle-aged. Viral CNS infections typically run an acute to subacute course but may be peracute (e.g., pseudorabies) or insidious (FIP) in onset and progression. Clinical signs of multifocal encephalopathy are common, but evidence of focal brain dysfunction may also occur. Extraneural signs (e.g., fever, ophthalmic disease, respiratory disease) of viral infections may or may not be present.

In canine distemper meningoencephalitis, historical or clinical evidence of gastrointestinal and/or respiratory disease prior to or concurrent with neurologic dysfunction are classic findings supportive of the diagnosis. Hyperkeratosis, or “hard pad,” affecting the foot pads and/or planum nasale is another classic, yet inconsistent indicator of canine distemper infection. Extraneural involvement is often either nonexistent or subclini-

cal and therefore not appreciated. Young (1 yr or less) dogs with CNS distemper infections tend to develop noninflammatory, primarily gray matter disease (polioencephalopathy), with predominant signs of forebrain dysfunction. Seizures are common with this form of canine distemper. Mature (more than 1 yr old) dogs with CNS distemper infections tend to develop inflammatory demyelinating white matter disease primarily affecting the brain stem, cerebellum, and spinal cord (leukoencephalomyelopathy). These latter patients tend to display predominant clinical signs of cerebellovestibular and/or spinal-cord dysfunction. A form of canine distemper CNS infection called "old dog encephalitis" is characterized primarily by forebrain dysfunction (e.g., behavior changes, visual deficits, circling) in middle-aged to older dogs (5 yr or older); this form of canine distemper is considered rare.

Myoclonus (repetitive, rhythmic muscular contraction) involving one or more limbs, and/or muscles of the head, is a relatively specific clinical finding in canine CNS distemper infection. Myoclonus is thought to be due to abnormal pacemaker activity in neurons damaged by the virus. "Chewing gum fits," rhythmic jaw movements displayed by some dogs with CNS distemper, may represent a form of myoclonus or focal seizure activity.

FIP (coronavirus) infection of the CSF is typically associated with the noneffusive form of the disease. Historical and clinical signs of systemic disease (e.g., fever, weight loss) are common in cats with coronavirus meningoencephalitis. Multifocal encephalopathy is common, often with brain-stem and cerebellar dysfunction.

A poor to nonexistent vaccination history in an acutely encephalopathic dog or cat with possible exposure to wildlife or other nonvaccinated dogs or cats should alert the clinician to consider rabies. The typical "furious" and "paralytic" forms of rabies have been described. The furious form is more common in cats and is characterized by apprehension and aggression, suggesting primarily forebrain dysfunction. The paralytic form, encountered more frequently in dogs, is characterized by LMN dysfunction of brain-stem nuclei, leading to a dropped jaw (CN V) and swallowing difficulty with attendant ptyalism (CN IX–XI). Respiratory difficulty and gait abnormalities may also be apparent. Focal and/or generalized seizure activity may occur with either form of rabies. Dogs and cats with rabies may present with a wide variety of clinical signs of neurologic dysfunction, and the above-mentioned forms of rabies should be viewed as very rough guidelines. It has been aptly stated that the only typical feature of the clinical signs of rabies is that they tend to be atypical.

Pseudorabies is rarely encountered in dogs and cats. A peracute onset and rapid progression (24–48 hr) of forebrain dysfunction (obtundation, seizures) is typically accompanied by hypersalivation, vomiting, diarrhea,

fever, and hyperpnea. A characteristic feature of canine and feline pseudorabies is intense pruritis over the head, neck, and shoulder areas.

FIV-associated encephalopathy has recently been reported, and may be more common than previously thought. Encephalopathy may occur in as many as one-third of FIV-infected cats. Affected cats typically exhibit signs of forebrain dysfunction such as behavior change (e.g., aggression) and compulsive pacing. Delayed righting reflexes and PLRs, as well as anisocoria have been observed in experimentally affected cats. Both experimentally and naturally infected cats tend to have minimally progressive or static signs of dysfunction for months; some cats even improve neurologically.

Clinical signs of feline Borna disease include progressive pelvic limb ataxia, sacral hyperesthesia, fever, loss of appetite, aggressiveness, staring activity, seizures, hypersensitivity to light and sound, inability to retract claws, and increased affection toward owners.

- c. Definitive diagnosis of viral meningoencephalitis is usually accomplished at necropsy. Identification of causative virus in brain parenchyma through various methods (e.g., visualizing inclusion bodies, immunocytochemistry, viral isolation) and the appearance of characteristic histologic patterns (e.g., pyogranulomas in FIP, demyelinating brain-stem lesions in canine distemper) help to confirm a diagnosis of a specific viral-induced encephalopathy. In the case of an unvaccinated dog or cat that has died or was euthanized because of brain disease (of recent onset) and has had exposure to people (especially bite wounds), examination of the brain (e.g., direct fluorescent antibody test) for rabies is mandatory. The ante-mortem diagnosis of viral meningoencephalitis is often difficult and relies on combining characteristic historical and clinical findings with several diagnostic tests. Specific and reliable diagnostic tests for viral meningoencephalitis are lacking. Intuitively, identifying the presence of a viral agent in a patient displaying encephalopathic signs would support that virus as being the causative factor. However, identifying virus or viral antigen in body tissues or fluids is usually unsuccessful.

The indirect fluorescent antibody test for canine distemper, usually performed on conjunctival scrapings, buffy coat smears, and/or urine sediment, may produce too many false negative and false positive results to be of much use. Identification of circulating antibody against various viruses in the blood and CSF can be readily accomplished. Since the patient may have been exposed naturally or intentionally (vaccination) to a suspect viral pathogen in the past, a positive serum antibody titer often has little clinical meaning. Similarly, in a patient previously immunized for a specific viral disease, demonstrating a positive titer in the CSF for that viral agent has little meaning. If the BBB is disrupted for any reason, the serum antibodies can passively move to the CSF. Demonstrating a gradient of titers (i.e., CSF titer for an antiviral antibody higher than the serum titer) is more definitive evidence of that virus as the causative agent.

More recently, the use of a one-step, reverse transcriptase, polymerase chain reaction (RT-PCR) test to amplify canine distemper virus-specific RNA products in serum and CSF has been described. This PCR procedure appears to be a specific antemortem test for canine distemper virus infection.

Some basic laboratory tests may provide supportive evidence for specific viral infections, if abnormal. Lymphopenia may occur with canine distemper infections, and hyperglobulinemia is common with FIP infections. Ophthalmic examination may provide valuable clinical evidence in some diseases (e.g., hyperreflective retinal lesions in canine distemper). CSF values are often abnormal with viral meningoencephalitis. Immature dogs with distemper affecting primarily grey matter may have normal CSF results. The characteristic CSF tap of a patient with CNS viral disease consists of predominantly mononuclear (lymphocytic) pleocytosis with elevated protein. The exception to this rule is CSF from FIP patients. The coronavirus tends to induce an intense immune response in this disease, and the predominant cell type in FIP meningoencephalitis is usually the neutrophil, with variable numbers of lymphocytes and macrophages (a pyogranulomatous response). In a recent report, many cases of neurologic FIP had normal CSF results. A high CSF IgG titer to feline coronavirus (greater than 1:25) was predictive of FIP as the cause of neurologic dysfunction in that study.

Advanced imaging (CT/MRI) is unlikely to reveal characteristic abnormalities in most cases of viral meningoencephalitis but may be useful to rule out other diseases (e.g., intracranial intra-arachnoid cysts in young dogs and cats). Hydrocephalus may be a common sequela to FIP meningoencephalitis that can be appreciated on a CT or MR image. Periventricular contrast enhancement has also been described in MR brain images of cats with FIP meningoencephalitis.

- d. There are no effective antiviral agents available for viral meningoencephalitis, and the prognosis for these diseases is generally poor to grave for survival. Rabies and pseudorabies are rapidly progressive and invariably fatal (often from respiratory failure) within one week and 48 hr, respectively. FIP typically progresses over several weeks and is also invariably fatal. Most dogs with CNS distemper infections die or are euthanized due to progressive neurologic dysfunction. However, clinical signs of disease may remain static or improve in some dogs, and survival is possible with proper nursing care. Anti-inflammatory doses of prednisone are often prescribed to lessen the secondary effects of viral infection on CNS tissue in these cases. FIV-associated encephalopathy appears to have a chronic course without progression of clinical signs in many cases. Although not yet reported in clinical cases, the use of zidovudine (AZT) at a dose of 50 mg per os, every 12 hr, has been recommended. Since this drug can cause myelosuppression, regular CBCs should be performed

while a cat is receiving this therapy. Cats with feline Borna disease typically exhibit progressively worsening neurologic dysfunction, necessitating euthanasia within 6 mo of onset of clinical signs.

4. Protozoal meningoencephalitis^{160,161,183,210-224}

- a. *Toxoplasma gondii* and *Neospora caninum* are protozoal agents known to occasionally cause meningoencephalitis in dogs. *Toxoplasma* has also been reported to cause meningoencephalitis in cats. Experimental infection of cats with *Neospora* may lead to meningoencephalitis, but no naturally occurring cases have been reported. The life cycles of *Toxoplasma* and *Neospora* are similar, the definitive hosts being cats and dogs, respectively. These protozoans are similar in many respects. Host infection is believed to occur transplacentally (tachyzoites), via ingestion of fecally shed oocysts (cats are the definitive hosts and shed oocysts), and/or ingestion of intermediate hosts containing the organisms (tachyzoites and bradyzoites). Neurologic dysfunction is thought to be caused by intracellular proliferation of tachyzoites. Recently, canine and feline meningoencephalitis due to an organism that appears to be *Sarcocystis* has been reported.
- b. Protozoal meningoencephalitis can occur at any age, but young animals seem more susceptible. The onset and progression of CNS dysfunction may be acute or chronic. Clinical signs reflecting either focal or multifocal encephalopathy are possible. Although these protozoal organisms tend to affect multiple organ systems, clinical signs are often reflective only of CNS disease. However, clinical evidence of a concurrent myopathy may be present in dogs with protozoal meningoencephalitis.
- c. Diagnosis of protozoal meningoencephalitis is based upon providing evidence of active protozoal infection in a patient with signs of encephalopathy. Further support of the diagnosis is obtained if the patient responds favorably to antiprotozoal medication. Identifying protozoal organisms in the living patient is unlikely, but there are several reliable tests to identify IgG antibodies against both *Toxoplasma* and *Neospora* in dogs and cats. There is no cross-reactivity between the antibody tests for these two organisms. Since dogs and cats may be exposed to these organisms (and hence produce a titer against them) without developing clinical disease, a single positive antibody titer does not establish a causal relationship. A fourfold increase in serum antibody titers over several weeks is supportive of active infection. CSF titers can also be performed and compared with serum titers (see Chapter 3). Also, IgM antibodies can be measured for *Toxoplasma* in addition to IgG. A positive IgM response with a negative IgG response suggests active infection.

Bloodwork may or may not reveal evidence of an inflammatory disease. Clinical evidence of ophthalmitis may be evident in some cases. CSF abnormalities are likely, and tend to be quite variable. Typically, a mixed-cell pleocytosis, primarily composed of neutrophils and mononuclear cells, with increased protein levels, is apparent. Predominantly mononu-

- clear pleocytosis, and normal CSF WBC counts with abnormal cellular distribution have also been reported with protozoal CNS infections.
- d. Clindamycin, or sulfonamides in combination with trimethoprim or pyrimethamine, are recommended for treating suspected or confirmed cases of protozoal meningoencephalitis. Clindamycin is recommended as a first-choice therapy for toxoplasmosis. A suggested dosage recommendation for clindamycin is 10 mg/kg per os, every 8 hr, for 2–4 wk. Trimethoprim-sulfa can be administered at a dosage of 15 mg/kg per os, every 12 hr, for 2–4 wk. An oral combination of sulfonamide (30 mg/kg, q 12 hr, for 2 wk) and pyrimethamine (0.25–0.5 mg/kg, q 12 hr) for 2 wk can also be implemented. Pyrimethamine is thought to be more effective than trimethoprim against *Toxoplasma*. Cats may develop myelosuppression while receiving prolonged (more than 2 wk) trimethoprim, sulfonamide, and pyrimethamine therapy, and may require folinic or folic acid replacement therapy. The prognosis for protozoal meningoencephalitis is guarded. Dogs and cats may survive if diagnosed and treated early in the course of the disease.
 5. Rickettsial meningoencephalitis^{161,225–229}
 - a. Neurologic dysfunction, including meningoencephalitis, can occur in as many as one-third of dogs with ehrlichiosis or Rocky Mountain spotted fever (RMSF). The causative agents of these disorders are *Ehrlichia canis* and *Rickettsia rickettsii*, respectively. These organisms are obligate intracellular parasites transmitted to dogs via the bites of infected ticks. Clinical signs of neurologic dysfunction may be due to vasculitis and/or hemorrhage in the CNS. Intracranial hemorrhages may be due to the vasculitis, as well as thrombocytopenia and platelet dysfunction characteristic of rickettsial disease. Feline rickettsial meningoencephalitis has not been reported.
 - b. Dogs of any age, sex, or breed can develop rickettsial meningoencephalitis, but German Shepherd dogs appear to be predisposed to rickettsial infection. There is often a history of potential or confirmed tick exposure. Onset of neurologic dysfunction is often acute and rapidly progressive. Focal and multifocal signs of encephalopathy may occur. Central vestibular disease is a common presentation. Clinical signs of systemic illness (e.g., fever, anorexia, lethargy) are common with rickettsial meningoencephalitis.
 - c. A tentative diagnosis of rickettsial meningoencephalitis is based on characteristic historical and clinical signs in a thrombocytopenic patient. Other bloodwork abnormalities may be appreciated, but thrombocytopenia is the most consistent. Antibodies to *Ehrlichia canis* and *Rickettsia rickettsii* can be measured in the serum and/or CSF. There is little cross-reactivity between the two organisms. A single, markedly elevated serum titer, in association with other supportive data, is highly suggestive of active rickettsial infection. Demonstration of a rising titer after several weeks is recommended, especially for RMSF. Appropriate treatment of ehrlichiosis

may result in a decreased convalescent titer. CSF titers can be compared with serum titers, as with other infectious diseases. CSF may reveal mainly mononuclear, mainly neutrophilic (suppurative), or a mixed pleocytosis. Because of the risk of hemorrhage in these patients, the procurement of CSF may not be advisable, especially if all other clinical evidence suggests rickettsial disease. A positive response to therapy also supports the diagnosis of rickettsial meningoencephalitis.

- d. Doxycycline, a tetracycline drug, is recommended for rickettsial meningoencephalitis, whether due to *Ehrlichia canis* or *Rickettsia rickettsii*, at an oral dosage of 10 mg/kg, every 12 hr, for 3 wk. Chloramphenicol is a viable alternative in very young (less than 6 mo, danger of teeth discoloration) dogs, or when doxycycline is ineffective. Enrofloxacin may be effective in RMSF cases, but appears to be ineffective in cases of ehrlichiosis. The prognosis for dogs with rickettsial meningoencephalitis is guarded to good, depending on the severity of neurologic dysfunction and the timeliness of therapeutic intervention.
6. Verminous meningoencephalitis^{161,183,230-244}
 - a. There are several reports describing aberrant parasitic migration to the brain of dogs and cats by organisms such as *Dirofilaria immitis*, *Baylisascaris procyonis* (raccoon roundworm), *Cuterebra*, and *Taenia serialis* (cystic coenurus formation in cats). Other parasites, such as *Ancylostoma*, *Toxascaris*, and *Angiostrongylus* also have potential for aberrant migration to the brain. The route of access to the host for most of these parasites is fecal-oral. In the case of *Cuterebra*, the small, first-stage larvae gain access through mucous-membrane-lined areas (e.g., the nose) or directly penetrate the skin. These parasites may cause neurologic dysfunction via a variety of mechanisms, including direct tissue damage and vascular compromise from migrating through brain parenchyma, inciting an intense inflammatory reaction by their presence, and the producing and releasing of neurotoxic and vasospastic substances. In general, these aberrant migrations are considered to be rare clinical phenomena. One potential exception is feline cuterebriasis. Recent data concerning *Cuterebra* migration in the brains of cats support this disease entity as the cause of feline ischemic encephalopathy (FIE), as well as a potential cause of other, poorly defined, feline seizure disorders.
 - b. Although there are no age limits for verminous meningoencephalitis, it tends to occur in young to middle-aged animals that have access to the outdoors. Clinical signs of neurologic dysfunction tend to be acute to peracute in onset, and may reflect focal or multifocal encephalopathy. In cats with cuterebriasis, asymmetric signs of focal forebrain dysfunction (e.g., behavior change, seizures, visual deficits) predominate, but clinical signs of a multifocal encephalopathy were apparent in 5 of 11 cases. A history of upper-respiratory disease was also common in these cats, possibly

reflecting the migration of the parasite through the nasal cavity toward the cribriform plate. These cats tend to present with signs of neurologic dysfunction between the months of July and September. Hyperthermia or hypothermia are common clinical findings in cats with CNS cuterebriasis. The rate of progression of feline cuterebriasis is not clear from the recently reported case series. Other case reports of verminous meningoencephalitis support a rapid progression of neurologic dysfunction.

- c. Definitive diagnosis of verminous meningoencephalitis depends upon identification of the causative parasite in the brain of an encephalopathic patient. To date, this has been accomplished at necropsy in all reported cases of verminous meningoencephalitis. In one feline *Cuterebra* case, the organism was not found, but other histopathologic evidence of its presence (parasite track, gliosis, infarction, laminar cerebrocortical necrosis) was apparent in the brain. *Cuterebra* organisms are most commonly located in the olfactory area of the brain in cats. The antemortem diagnosis depends primarily on clinical suspicion. Bloodwork abnormalities are often nonexistent or nonspecific. CSF evaluation has been reported in only several cases; in two of three cats with CNS cuterebriasis, the CSF was abnormal, with mononuclear pleocytosis and elevated protein. One of these two cats had 8% eosinophils in the CSF WBC differential count. The use of advanced imaging (CT/MRI) has been reported in one definitively diagnosed case of feline CNS cuterebriasis. The CT of this cat showed the brain to have a mottled appearance with no discrete mass lesions. Advanced imaging may become an important diagnostic tool in the antemortem diagnosis of verminous meningoencephalitis.
- d. In general, treatment options for verminous meningoencephalitis are limited and the prognosis is grave. The prognosis for feline cuterebriasis is unknown, as antemortem diagnosis is difficult and reports of definitive treatment of tentatively diagnosed cases are limited. The recently reported case series was based on retrospective evaluation of necropsy cases, so these cases may reflect the most severely affected cats. Cats with seizure disorders and CSF evidence of nonsuppurative meningoencephalitis generally respond favorably for long time periods to treatment with anticonvulsants and prednisone. *Cuterebra* larvae are thought to be susceptible to ivermectin, and a treatment protocol has been suggested for cats with suspected cuterebriasis (a single SQ ivermectin dose of 400 µg/kg). Pretreatment (1–2 hr prior) with diphenhydramine (4 mg/kg), and intravenous dexamethasone (0.1 mg/kg) administered at the time of ivermectin injection are recommended to prevent or mitigate allergic/anaphylactic reactions to dead or dying larvae. A two-week course of prophylactic antibiotic therapy is also recommended to help prevent secondary bacterial meningoencephalitis. Although not yet reported, surgical removal of intracranial *Cuterebra* in cats may be another viable therapeutic option for

feline cuterebriasis-associated meningoencephalitis, alone or in addition to ivermectin therapy.

7. Miscellaneous infectious meningoencephalitides^{205,245–254}

- a. There are a number of infectious agents that have been rarely reported to cause CNS disease in dogs and cats. Included among these are *Prototheca* (an alga), *Borrelia burgdorferi* (the spirochete responsible for Lyme disease) in dogs, and suspected scrapie-infection in cats in the United Kingdom (feline spongiform encephalopathy). *Prototheca* is an environmental contaminant that may invade immunocompromised animals. *Borrelia* is transmitted via *Ixodid* ticks in endemic areas (e.g., New England). Feline spongiform encephalopathy (FSE) is thought to develop after cats ingest food contaminated with the bovine spongiform encephalopathy (BSE) agent.
- b. Because of the paucity of reported cases, little is known about typical signalment and historical findings in dogs and cats with CNS protothecosis or borreliosis. Collies may be predisposed to disseminated protothecosis, and dogs with suspected borreliosis may have a history of tick exposure and/or having lived in or visited a Lyme-endemic area. Reports of cats with FSE have been primarily limited to Great Britain. These cats tend to start exhibiting clinical signs of neurologic dysfunction at about 5 yr of age. As with other animals infected with scrapie, a long incubation period is suspected for FSE. Animals with protothecosis and borreliosis tend to exhibit clinical signs of extraneural disease. Bloody diarrhea is a frequent finding in disseminated protothecosis, and arthritis involving one or more limbs is a hallmark of borreliosis. Focal and multifocal/diffuse, progressive encephalopathy can result from protothecosis, borreliosis, and FSE.
- c. Antemortem diagnosis of these infectious diseases is uncommon and depends primarily on historical findings and clinical signs. *Prototheca* may cause a mixed-cell (neutrophils and lymphocytes) CSF pleocytosis. FSE is a noninflammatory disease, and CSF pleocytosis is unlikely. CSF findings in CNS borreliosis are poorly defined. In one reported dog with suspected CNS borreliosis, CSF values were within normal limits. Demonstration of CSF antibodies against *Borrelia* in excess of those found in the serum is highly suggestive of CNS borreliosis. *Prototheca* may be identified by examining body fluids or tissue aspirates/biopsies, and/or by culturing these samples for the organism. Definitive diagnosis of CNS protothecosis and FSE is typically made at necropsy.
- d. There is no known effective treatment for FSE and the disease is uniformly fatal. Efforts to eliminate BSE in the United Kingdom will likely result in disappearance of the feline disease. Although a number of anti-fungal agents have been advocated to treat disseminated protothecosis, this disease is virtually invariably fatal, despite therapy. Antibiotics such as doxycycline, amoxicillin, and third-generation cephalosporins have shown activity against *Borrelia*, but their efficacy in treating dogs with CNS borreliosis is currently unknown.

8. Granulomatous meningoencephalomyelitis (GME)^{160,161,183,252,255–261}
 - a. A common idiopathic inflammatory disease of the CNS in dogs (extremely rare in cats), GME is characterized histologically by perivascular infiltrates of primarily mononuclear cells (lymphocytes, macrophages, and plasma cells) in the brain and/or spinal cord. The characteristic perivascular cellular infiltrates of GME both define the disease syndrome and account for the neurologic deficits. Although the underlying cause of this disease remains a mystery, there is evidence that GME represents an autoimmune disorder, specifically a delayed-type (T cell-mediated) hypersensitivity reaction.
 - b. GME can affect any breed of dog of any age and either sex. However, young to middle-aged (median age of 5 yr) female dogs of small breeds (e.g., Poodles, terriers) appear to be predisposed. Clinical signs of either focal or multifocal CNS dysfunction are possible. Multifocal (often called disseminated) GME is characterized by acute onset and rapid progression of CNS dysfunction, whereas dogs with focal GME tend to have a more insidious onset and slower progression of clinical signs. Whether alone (focal GME) or in combination (multifocal GME), seizures, cerebellovestibular dysfunction, and cervical hyperesthesia are common features of GME. Isolated spinal-cord dysfunction and optic neuritis are relatively uncommon clinical presentations of GME. Patients with GME may occasionally be febrile upon presentation.
 - c. A definitive diagnosis of GME is based upon characteristic histopathologic features of affected brain and/or spinal-cord tissue. Although there are reports of biopsy-confirmed cases of GME in dogs with focal cerebral lesions, the vast majority of confirmed GME cases have been diagnosed via necropsy. Antemortem diagnosis of GME is based upon characteristic signalment, historical and clinical findings, as well as results of diagnostic tests. CSF evaluation usually provides the most important information in the antemortem diagnosis of GME. A mainly mononuclear pleocytosis, with a variable percentage of neutrophils (mean of about 20%) and elevated protein level, is characteristic of GME. Uncommonly (10% or less), GME patients will have primarily neutrophilic or normal CSF results. Results of imaging studies are highly variable in dogs with GME. CT/MR images of the brain in GME patients may be normal, may show solitary (Fig. 4.22) or multiple (Fig. 4.23) circumscribed mass lesions, or may reveal areas of contrast enhancement with indistinct margins (Fig. 4.24). Some dogs with GME have secondary hydrocephalus evident on CT/MR images of the brain.
 - d. Immunosuppressive glucocorticoid therapy (e.g., oral prednisone, 1–2 mg/kg, q 12 hr) is the standard treatment protocol for GME. The dose may be slowly reduced over time if the patient exhibits a clinical response to treatment. However, GME patients typically require lifelong immunosuppressive therapy. The author has successfully used azathioprine in sev-



Fig. 4.22. Transaxial (A) and dorsal (B), contrast-enhanced CT brain images of a dog with focal GME of the occipital lobe. The lesion was surgically resected.

eral presumptive GME patients, allowing reduction or elimination of glucocorticoid treatment. Megavoltage radiation therapy has shown some efficacy in cases of focal GME. There is limited, largely anecdotal evidence of efficacy for the drugs leflunomide and procarbazine in GME. These



Fig. 4.23. Dorsal contrast-enhanced CT brain image of a dog with multifocal GME. Note the multiple areas of circumscribed contrast enhancement.



Fig. 4.24. Dorsal contrast-enhanced CT brain image of a dog with multifocal GME. Note the areas of contrast enhancement with indistinct margins.

drugs are relatively specific for T cells. GME patients with seizure activity should be treated with anticonvulsant drugs.

The prognosis for definitively diagnosed cases of GME is poor. In a recent report, the median survival time for dogs with GME was 14 days. Dogs with focal GME had significantly longer survival times (median of 114 days) than those with multifocal GME (median of 8 days) in that study. Dogs with clinical signs of focal forebrain dysfunction had the longest survival times (more than 395 days). Although the prognosis for GME appears to be poor, the clinician must bear in mind that the mortality statistics for this disease are based primarily on necropsy cases. The prognosis for presumptively diagnosed (i.e., no necropsy or brain biopsy) cases of GME has not been investigated. The author has treated a large number of suspected GME cases that have survived for relatively long time periods (over 1 yr). In other words, since a definitive diagnosis of GME is typically based upon a necropsy report, mortality statistics for this disease may be biased toward the most severe cases. Because of this, aggressive treatment of the suspected GME patient is recommended, despite the poor prognosis associated with this disease.

9. Necrotizing meningoencephalitis of small-breed dogs^{160,161,183,252,262-267}

- a. An idiopathic, necrotizing meningoencephalitis, primarily affecting the cerebral hemispheres, has been described in Pug and Maltese dogs (Pug/Maltese meningoencephalitis). A syndrome with similar necrotic lesions on histopathologic evaluation, but with a different lesion distribution (brain-stem lesions in addition to cerebral lesions) has been described in the Yorkshire terrier breed (Yorkshire terrier meningoencephalitis). A syndrome similar to Pug/Maltese meningoencephalitis has been mentioned in a Chihuahua, and the author has also encountered a similar necrotizing meningoencephalitis in a Boston terrier. It is expected that more breeds will be reported with idiopathic necrotizing meningoencephalitis. As with GME, the necrotic lesions observed on brain histopathology both account for the clinical signs of dysfunction and define the disease syndrome. Although the cause is unknown, the brain lesions are reminiscent of alpha herpes virus meningoencephalitis of people.
- b. Pug and Maltese dogs with necrotizing meningoencephalitis have varied in age at presentation between 6 mo and 7 yr. The onset and progression of clinical signs of neurologic dysfunction may be acute (disease course of 2 wk or less) or chronic (disease course of 4-6 mo). Clinical signs of forebrain dysfunction (seizures, circling, obtundation, visual deficits with normal PLRs, head-pressing, etc.) predominate. Neck pain is also common and may be due to the meningitis and/or the forebrain disease.

Yorkshire terriers with necrotizing meningoencephalitis have been reported between the ages of 1 and 10 yr. These dogs typically experience a chronic, progressive worsening of neurologic dysfunction over several

months. In addition to clinical signs of forebrain dysfunction and neck pain, Yorkshire terriers with necrotizing meningoencephalitis often display clinical signs of brain-stem dysfunction (e.g., central vestibular disease).

- c. The definitive diagnosis of small-breed necrotizing meningoencephalitis is based upon characteristic histopathologic brain lesions observed at necropsy. A tentative diagnosis is based primarily upon signalment, history, and findings of the neurologic examination. Bloodwork results are typically normal. CSF findings are often abnormal; most commonly, a predominantly or exclusively mononuclear pleocytosis with elevated protein levels is evident. The mononuclear cells in Pug/Maltese meningoencephalitis are usually primarily lymphocytic, whereas a mixture of lymphocytes and monocytes is usually seen in the CSF of Yorkshire terrier meningoencephalitis patients. In one Maltese dog with necrotizing meningoencephalitis, one-half of the cells in the CSF differential were neutrophils.

CT/MR findings have been described in several cases of necrotizing meningoencephalitis. Asymmetric ventricular dilation, and areas of radiolucency in the brain (corresponding with malacic brain parenchyma), sometimes appearing continuous with the lateral ventricles, are consistent findings (Fig. 4.25). In one Maltese dog, a contrast-enhancing lesion was identified in the cerebrum. In all other reported cases of necrotizing meningoencephalitis in which imaging was performed, contrast-enhancement of brain lesions was lacking.

- d. Treatment of suspected necrotizing meningoencephalitis patients with glucocorticoids and anticonvulsant drugs (if seizing) should be attempted, but usually has little to no appreciable clinical effect. The

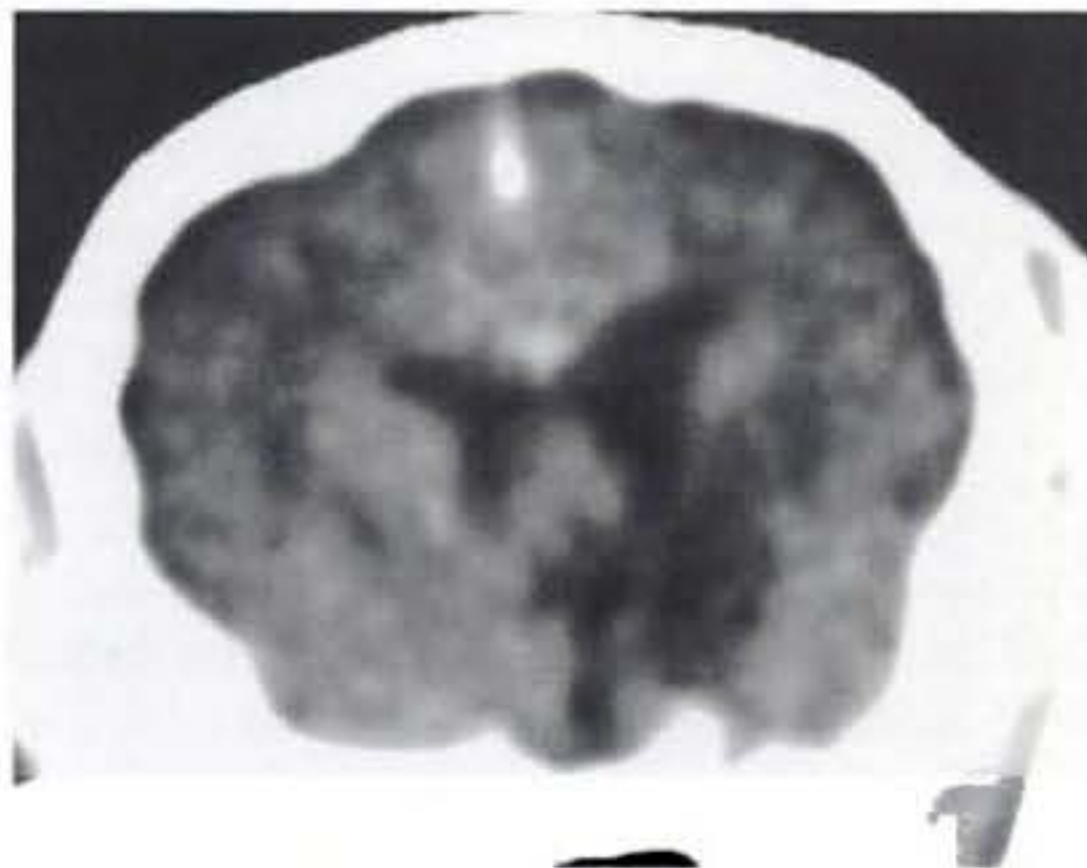


Fig. 4.25. Transaxial contrast-enhanced CT brain image of a Yorkshire terrier with necrotizing meningoencephalitis. Note the regions of parenchymal radiolucency (Courtesy of Dr. Mike Walker).

prognosis for necrotizing meningoencephalitis is poor to grave. Although one Yorkshire terrier with necrotizing meningoencephalitis survived for 18 mo, the majority of dogs die or are euthanized due to progressive neurologic dysfunction within 6 mo of onset of neurologic dysfunction. The author recently treated a Pug dog with suspected necrotizing meningoencephalitis with mycophenolate mofetil (CellCept-Roche pharmaceuticals). The patient was responding poorly to glucocorticoid therapy, and clinical signs stabilized shortly after CellCept initiation. The dog was alive and doing well at last follow-up, 8 mo after treatment initiation.

10. Eosinophilic meningoencephalitis²⁶⁸⁻²⁷⁰

- a. A rare, idiopathic meningoencephalitis, characterized by eosinophilic pleocytosis of the CSF has been described in nine dogs and one cat. No infectious agents were identified to account for the meningoencephalitis, and a type I hypersensitivity reaction is suspected. Eosinophils can release substances that are directly neurotoxic, which may explain some of the clinical signs of dysfunction in these patients, as well as the variable response to treatment.
- b. The dogs reported with eosinophilic meningoencephalitis varied in age at onset of clinical signs from 4 mo to 5.5 yr. Three of the nine dogs were Golden retrievers, two were Rottweilers, and one was a Rottweiler cross-bred dog. The reported cat (domestic shorthaired breed) was 6 yr old at the time of clinical disease onset. All reported cases were male. Neurologic dysfunction developed over one to several weeks in most of the animals, although one dog had a 6-mo history of intermittent seizure activity. Eight of the nine dogs exhibited clinical signs suggesting forebrain dysfunction (e.g., circling, obtundation, seizure activity). Three of these dogs also had evidence of brain-stem disease (gait deficits, facial paresis, decreased gag reflex). One dog demonstrated cerebellovestibular (head tremors, hypermetric gait, head tilt) and spinal cord (diminished patellar reflex) dysfunction. The cat with eosinophilic meningoencephalitis exhibited signs of forebrain and brain-stem dysfunction.
- c. The diagnosis of eosinophilic meningoencephalitis is based upon demonstrating an eosinophilic CSF pleocytosis in an encephalopathic patient, with no apparent inciting cause. In people, a CSF pleocytosis is considered eosinophilic if the eosinophils comprise more than 10% of the WBC differential. The eosinophil percentage in the reported veterinary cases varied between 55% and 100%. Since histopathologic lesions have been described for only two dogs with eosinophilic meningoencephalitis, there is no defined histopathologic pattern upon which to base a definitive diagnosis. Seven of the nine reported dogs had peripheral eosinophilia evident on a CBC evaluation.
- d. The appropriate therapy for this enigmatic syndrome is unclear. However, four of the nine dogs and the cat recovered with glucocorticoid therapy. One of the dogs recovered after treatment with chloramphenicol, and one

dog improved with a combination of amoxicillin/clavulanic acid and prednisone. From this limited information, it appears that the prognosis for survival is fair with eosinophilic meningoencephalitis.

11. Hydrocephalus with periventricular encephalitis (HPE)^{252,271–273}

- a. A rare form of meningoencephalitis has been described in puppies. This idiopathic disease is characterized by hydrocephalus and intense inflammatory and hemorrhagic lesions in the brain parenchyma, especially in subependymal locations. Although the etiology of this syndrome is unknown, a bacterial cause is suspected.
- b. This syndrome tends to occur in puppies 2–3 mo of age. A wide variety of breeds, including large-breed dogs, have been reported. Onset of neurologic deficits is acute and the progression is typically rapid. Clinical signs of forebrain disease (e.g., behavior change, blindness, circling) predominate, but signs of brain-stem dysfunction (e.g., head tilt, ataxic gait) are also often appreciated. Progressive enlargement of the skull may also be appreciated in these puppies.
- c. A definitive diagnosis of HPE is based upon gross and histopathologic examination of the brain at necropsy. A presumptive diagnosis is based upon typical signalment, history, and clinical signs, as well as evidence of hydrocephalus. CSF analysis may reveal a mixed-cell pleocytosis, increased protein, and xanthochromia.
- d. The sparse literature pertaining to this disease syndrome is primarily based upon pathology findings. This appears to be a rapidly progressive, usually fatal disease. However, in some dogs, the disease may stabilize. The appropriate therapy for this condition is unknown. Combination antibiotic/corticosteroid therapy, with or without surgical shunting for hydrocephalus should be considered in puppies with this disease syndrome. The author has recently reported successful medical and surgical (i.e., ventriculoperitoneal shunting) management of a suspected HPE case with external hydrocephalus (Fig. 4.26).

G. Ischemic/vascular^{2,274–282}

1. Brain ischemia refers to a diminished blood supply to the brain of sufficient magnitude to cause signs of encephalopathy. Such ischemia may be relatively global, as with cardiac insufficiency, severe pulmonary disease, or diffuse brain swelling following toxic or traumatic insult to the brain. Global brain ischemia also occasionally occurs in association with anesthetic “accidents” (insufficient oxygen delivery to the patient), or anesthesia-related cardiopulmonary arrest. Areas of the brain particularly prone to global hypoxia/ischemia include the cerebral cortex, hippocampus, basal nuclei, thalamic nuclei, and Purkinje cells of the cerebellum.

Most cases of ischemic/vascular encephalopathy are focal events. Focal (usually) or multifocal brain ischemia may occur with intracranial hemorrhage and/or infarction. An infarct is a focal occlusion of one or more blood

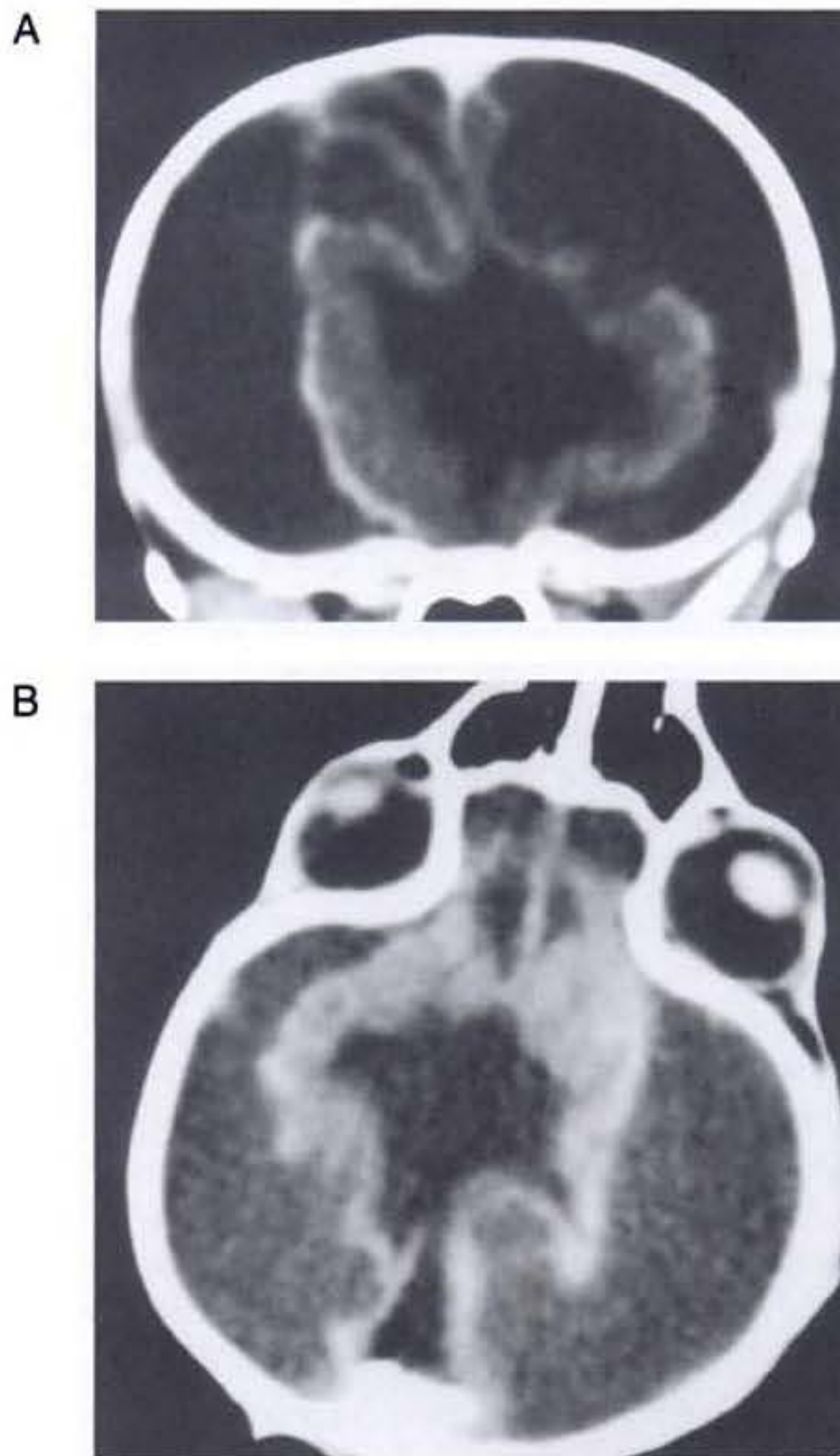


Fig. 4.26. Transaxial (A) and dorsal (B) contrast-enhanced CT brain images of a dog with external hydrocephalus and suspected periventricular encephalitis (HPE). Note the extra-axial fluid accumulation around the brain (Reprinted with permission²⁷³).

vessels (usually arterial), resulting in an area of compromised brain parenchyma. An infarct may be due to vascular obstruction that develops within the occluded vessel (thrombosis), or due to obstructive material that originates from another vascular bed and travels to the brain (embolism). Focal hemorrhage may accompany brain thromboembolism due to disruption of the wall(s) of the occluded vessel(s). Thromboembolic brain disease in people is usually due to atherosclerosis, a syndrome in which there is progres-

sive deposition of lipids and cholesterol in the tunica media and tunica intima of arterial vessels throughout the body. Although occasionally reported in association with canine hypothyroidism, atherosclerosis is considered extremely rare in companion animals. Septic and neoplastic emboli can travel to the brain and cause infarcts. Thromboembolic disease may also be associated with cardiac disorders such as cardiomyopathy. Aberrant parasite migration leading to vascular compromise of the brain was discussed earlier in this chapter. Feline ischemic encephalopathy (FIE) is an asymmetric, peracute vascular disease primarily affecting the forebrain. There is now substantial evidence to support *Cuterebra* migration as the cause of this disorder.

Systemic hypertension from a variety of causes (e.g., pheochromocytoma, renal failure, hyperadrenocorticism, feline hyperthyroidism, diabetes mellitus) can result in brain parenchymal hemorrhages and clinical signs of encephalopathy. Other causes of brain hemorrhage include vasculitis (e.g., rickettsial infections), coagulation disorders (e.g., rodenticide toxicity), neoplasia, and trauma.

Regardless of the cause of an ischemic/vascular injury to the brain, neuronal dysfunction ensues due to factors such as oxygen-free radical production, anaerobic metabolism and lactate production, and loss of cellular osmotic equilibrium.

2. Signalment, as well as historical and clinical findings, are extremely variable in this category of encephalopathy, due to the number of possible causative diseases. Ischemic/vascular events affecting the brain typically cause acute/peracute onset of focal, asymmetric encephalopathy. Forebrain dysfunction is most common, but brain-stem and/or cerebellar dysfunction may occur. As mentioned earlier, diffuse brain dysfunction may occur with cardiac failure, severe pulmonary disease, toxins, severe brain injury, and anesthetic mishaps. Seizures and vision loss (often permanent) are likely sequelae to such global ischemia. The clinical signs of neurologic dysfunction in dogs and cats with focal ischemic/vascular brain disorders tend to either remain static or improve with time.
3. Diagnosis of ischemic/vascular encephalopathy depends upon ruling out other causes of focal encephalopathy and identifying an underlying disease state that could cause an ischemic/vascular event. A history of an acute/peracute onset of asymmetric encephalopathy that improves over time is suggestive of an ischemic/vascular etiology. A specific diagnosis for the underlying cause of the ischemic/vascular event should be sought. A discussion of these diseases is beyond the scope of this text. Advanced imaging (CT/MR) may reveal focal lesions in cases of ischemic/vascular encephalopathy (Fig. 4.27), but these lesions can be difficult to discern from other disease processes (e.g., neoplasia) without a biopsy sample. Advanced imaging may be normal in cases of global ischemia, or may reveal evidence of diffuse edema and/or contrast uptake in susceptible areas of the brain (Fig. 4.28). CSF evaluation may



Fig. 4.27. Transaxial (A) and sagittal (B) MR brain images (T1-weighted with contrast) of a dog with a focal cerebral infarct.

or may not be abnormal and is not likely to render a specific diagnosis in most cases.

4. The treatment of ischemic/vascular encephalopathy is similar to that for victims of severe head trauma (see Chapter 5). In addition to therapy directed at combating brain swelling (e.g., mannitol), therapy directed at controlling the causative disease process (if identifiable) should also be instituted. The prognosis for ischemic/vascular encephalopathy is extremely variable, and depends primarily on the underlying cause of the encephalopathy.

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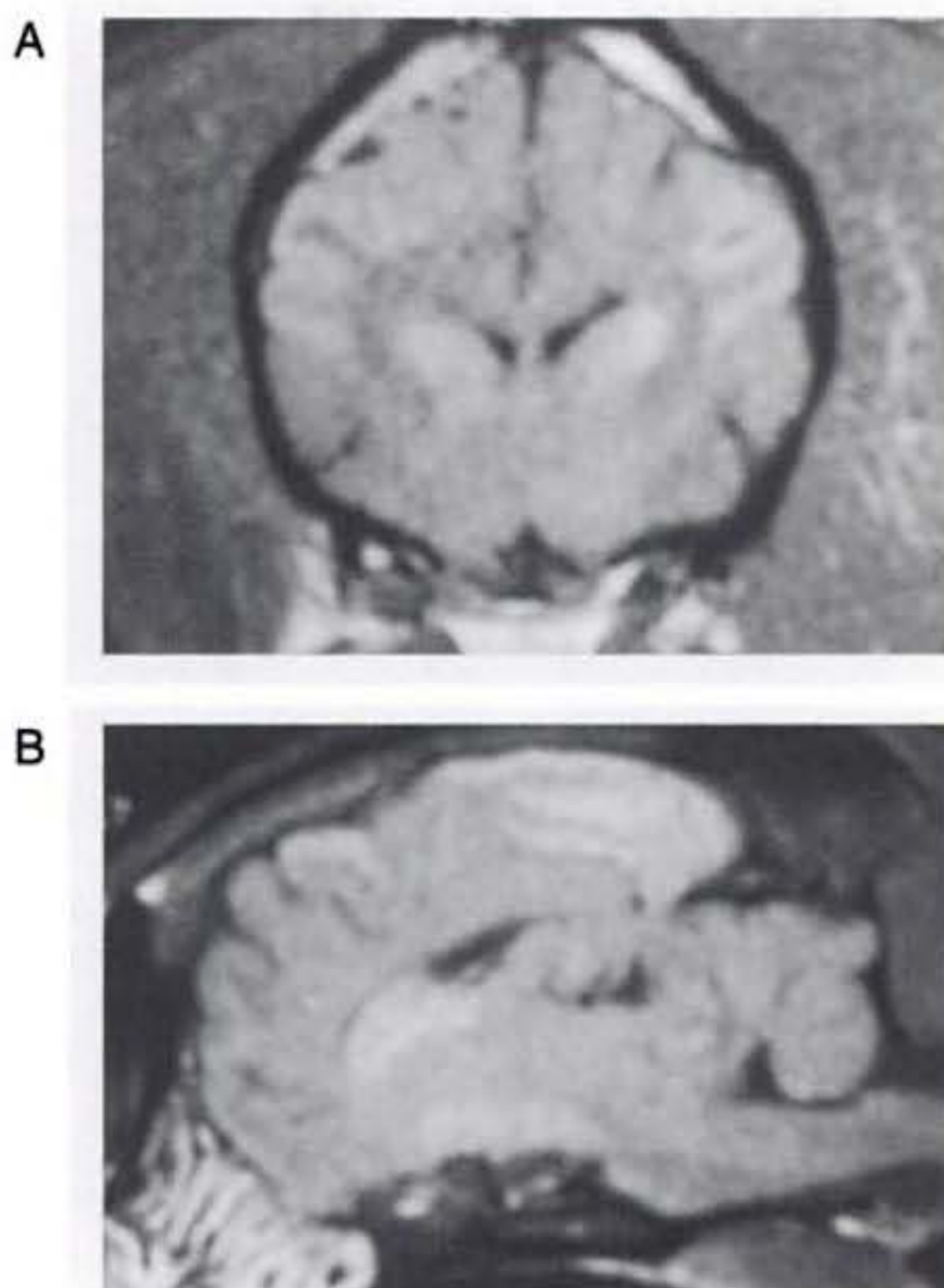


Fig. 4.28. Transaxial (A) and sagittal (B) MR brain images (T1-weighted with contrast) of a dog that experienced anesthetic-related brain ischemia/hypoxia. Note the diffuse contrast uptake in the cerebral cortical and caudate nucleus/rostral thalamic regions.

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Chapter 5

HEAD-TRAUMA MANAGEMENT

Curtis W. Dewey

I. Introduction¹⁻⁴

Severe head trauma is associated with a high degree of mortality in humans and animals. Death typically results from progressive increases in intracranial pressure (ICP). Brain injury in dogs and cats is most often due to automobile trauma; other causes include missile injuries (e.g., gunshot wounds), animal bites, and falls. Considerable controversy exists concerning therapy of severely brain-injured patients and this field is one of intense research in human neurology/neurosurgery. This chapter contains recent information regarding therapy for head-trauma victims. Retrospective and prospective clinical data pertaining to the treatment of canine and feline head trauma are lacking, so most of the clinical recommendations in this chapter are based upon information from human head-trauma studies and experimental head-trauma investigations. Opinions differ concerning what constitutes appropriate therapy for the severely brain-injured pet. However, few would argue that treatment needs to be expedient and aggressive for the majority of these patients. The first veterinarian the brain-injured pet encounters after the traumatic incident will likely dictate the eventual outcome for that patient. Dogs and cats can function well with considerable loss of cerebral tissue, if given time to recover from a severe brain injury. The ultimate goal in head-trauma management is to return the patient to the role in society occupied prior to the injury. It is of utmost importance to alleviate brain swelling and prevent damage to vital brain-stem structures.

II. Pathophysiology of Head Trauma¹⁻¹⁰

Brain injury can be conceptually divided into primary and secondary injury. Primary brain injury occurs immediately following impact and instigates a number of inflammatory cascades, which result in secondary brain injury. Both primary and secondary brain injury contribute to increased ICP. A basic understanding of the mechanisms of brain-tissue damage following injury and ICP dynamics is essential to logical therapy of the severely head-traumatized patient.

A. Primary brain injury

This type of injury refers to the physical disruption of intracranial structures that occurs immediately at the time of the traumatic event. Such injury includes direct damage to brain parenchyma, such as contusions, lacerations, and diffuse axonal injury. Damage to blood vessels may result in intracranial hemorrhage (Fig. 5.1) and vasogenic edema. The extent of primary brain injury is a function of the force of impact. Acceleratory and deceleratory forces of both the impacting

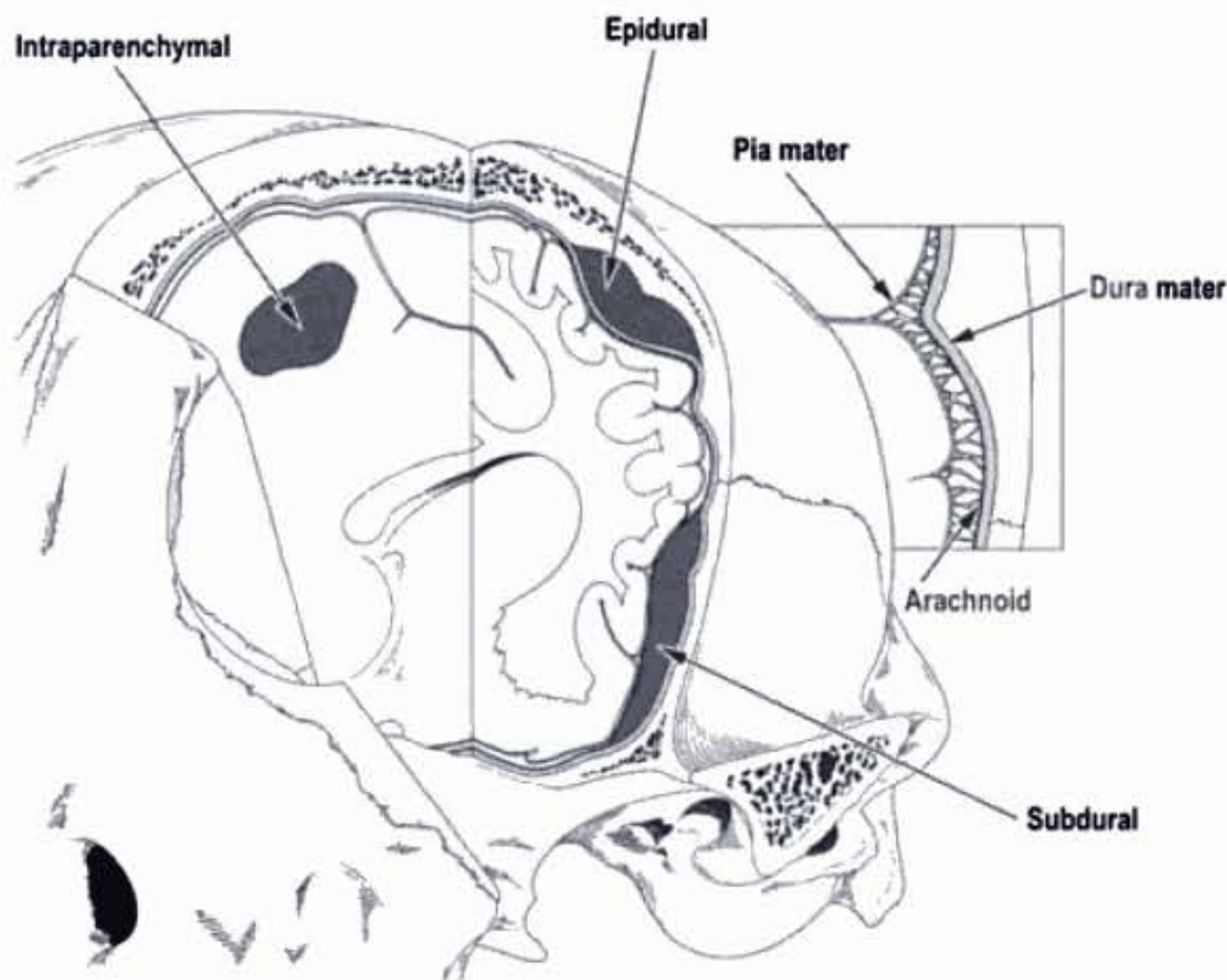


Fig. 5.1. Clinically important forms of intracranial hemorrhage. Subarachnoid hemorrhage (not depicted) would occur as diffuse hemorrhage between the pia and arachnoid layers (see inset)(Illustration by Anton Hoffman).

object(s) and the intracranial contents will affect overall tissue damage. Direct parenchymal damage associated with primary brain injury is beyond the control of the clinician.

B. Secondary brain injury

In addition to continued hemorrhage and edema, the damage caused by the primary brain injury activates a number of interrelated biochemical pathways that act in concert to perpetuate further brain-tissue damage and subsequent increases in ICP. Adenosine triphosphate (ATP) depletion disrupts the maintenance of cellular ionic homeostasis. Sudden, uncontrolled intracellular influx of sodium (Na^+) and calcium (Ca^{++}) occurs. Cellular swelling (cytotoxic edema) and depolarization result. The uncontrolled depolarization leads to large amounts of glutamate, an excitatory neurotransmitter, to be released into the extracellular environment. Glutamate causes further increases in intracellular Ca^{++} levels. Elevated Ca^{++} levels activate a number of tissue-damaging pathways, including the arachidonic acid cascade (phospholipase A_2 activation) and the xanthine oxidase (free-radical producing) pathway. Iron (Fe^{++}) is a vital cofactor in the xanthine oxidase pathway, and free radical species (e.g., hydroxyl and superoxide radicals) are preferentially damaging to cell membranes containing high levels of polyunsaturated fats (PUFAs) and cholesterol. Brain tissue is rich in both Fe^{++} and membranes with high levels of PUFAs and cholesterol. Free radical species are

thus particularly damaging to neuronal membranes and probably play a major role in secondary brain injury. Their production is also induced by ischemia, arachidonic acid metabolites, catecholamine oxidation, and activated neutrophils. Other secondary autolytic processes induced after severe head trauma include the complement, kinin, and coagulation/fibrinolytic cascades. Elevated levels of nitric oxide (NO) and various cytokines (e.g., tumor necrosis factor, interleukins) also contribute to parenchymal injury in the damaged brain. Most of the mediators of tissue damage produced by these various reactions perpetuate their own continued production as well as the production of other mediators. The maintenance of an ischemic environment perpetuates the above-mentioned processes and also leads to the accumulation of lactic acid (via anaerobic glycolysis). Lactic acid accumulation leads to further damage to brain tissue. Hypotension and hypoxemia, extracranial conditions that are common in the traumatized patient, can worsen brain ischemia and thereby enhance the events responsible for secondary brain injury. The end result of these secondary processes is increased ICP. Unlike primary brain injury, the clinician has some control over secondary brain injury.

C. Intracranial pressure (ICP) dynamics

Intracranial pressure (ICP) is the pressure exerted by tissues and fluids within the cranial vault. Normal ICP values for dogs and cats range between 5 and 12 mm Hg. Cerebral perfusion pressure (CPP) is a primary determinant of cerebral blood flow and hence brain oxygenation and nutritional support. CPP is defined by the following equation:

$$\text{CPP} = \text{MABP} - \text{ICP} \quad (\text{MABP} = \text{mean arterial blood pressure})$$

The normal contents of the cranial cavity include brain parenchyma, blood, and cerebrospinal fluid (CSF). In the normal animal, these components exist in equilibrium with each other and ICP remains within normal limits. Between the MABP extremes of 50–150 mm Hg, ICP remains constant. This phenomenon is called *pressure autoregulation*. Pressure autoregulation serves to link systemic blood pressure changes to brain vasculature tone. If MABP rises, vasoconstriction occurs in the brain; if MABP falls, vasodilation occurs in the brain. In the normal animal, the former scenario prevents ICP from rising, and in the latter, prevents ICP from falling. *Chemical autoregulation* refers to the direct responsiveness of brain vasculature to the partial pressure of carbon dioxide in arterial blood (PaCO_2); elevated PaCO_2 levels cause vasodilation, whereas decreased PaCO_2 levels cause vasoconstriction. Both forms of autoregulation often remain intact in people with severe head injury, but pressure autoregulation may be compromised in approximately 30% of patients. In some of these individuals, the lower MABP extreme may become “reset” to a higher value. With severe head trauma, both intracranial hemorrhage and edema can add to the volume of the intracranial compartment. Due to the inexpandable nature of the skull, one or more components of the cranial cavity must accommodate for the increased volume, or increased ICP will result.

This accommodation or volume buffering is accomplished by fluid shifts in the brain vasculature and CSF pathways and is referred to as *intracranial compliance*. Compliance is expressed as the change in volume per unit change in pressure. Intracranial compliance has limitations, and decreases as ICP increases. If intracranial volume increases beyond the abilities of compensatory mechanisms, progressively larger increases in ICP result per unit of volume increase (Fig. 5.2), CPP is compromised, and ischemic death of brain tissue occurs. In cases of severe head trauma, intracranial compliance often is quickly exhausted. If MABP decreases (hypotension), especially in combination with hypoxemia, the brain vasculature will vasodilate in an effort to preserve blood flow. The increase in blood volume increases ICP, but CPP remains inadequate. In addition, the secondary autolytic processes occurring in the injured brain are enhanced by hypotension and hypoxemia, and further brain injury and edema occur with a resultant rise in ICP.

III. Initial Assessment and Emergency Treatment^{1,3,11-22}

Initial physical assessment of the severely brain-injured patient focuses on imminently life-threatening abnormalities. Many patients suffering severe head trauma present to the clinician in a state of hypovolemic shock. Do not be in a rush to focus initially on the patient's neurologic status; it may well improve once the shock state is corrected. Remember that traumatized, hypovolemic patients with no appreciable brain injury often exhibit depressed mentation, due primarily to the hypotensive state. The clinician must first focus on the ABCs of trauma management (airway,

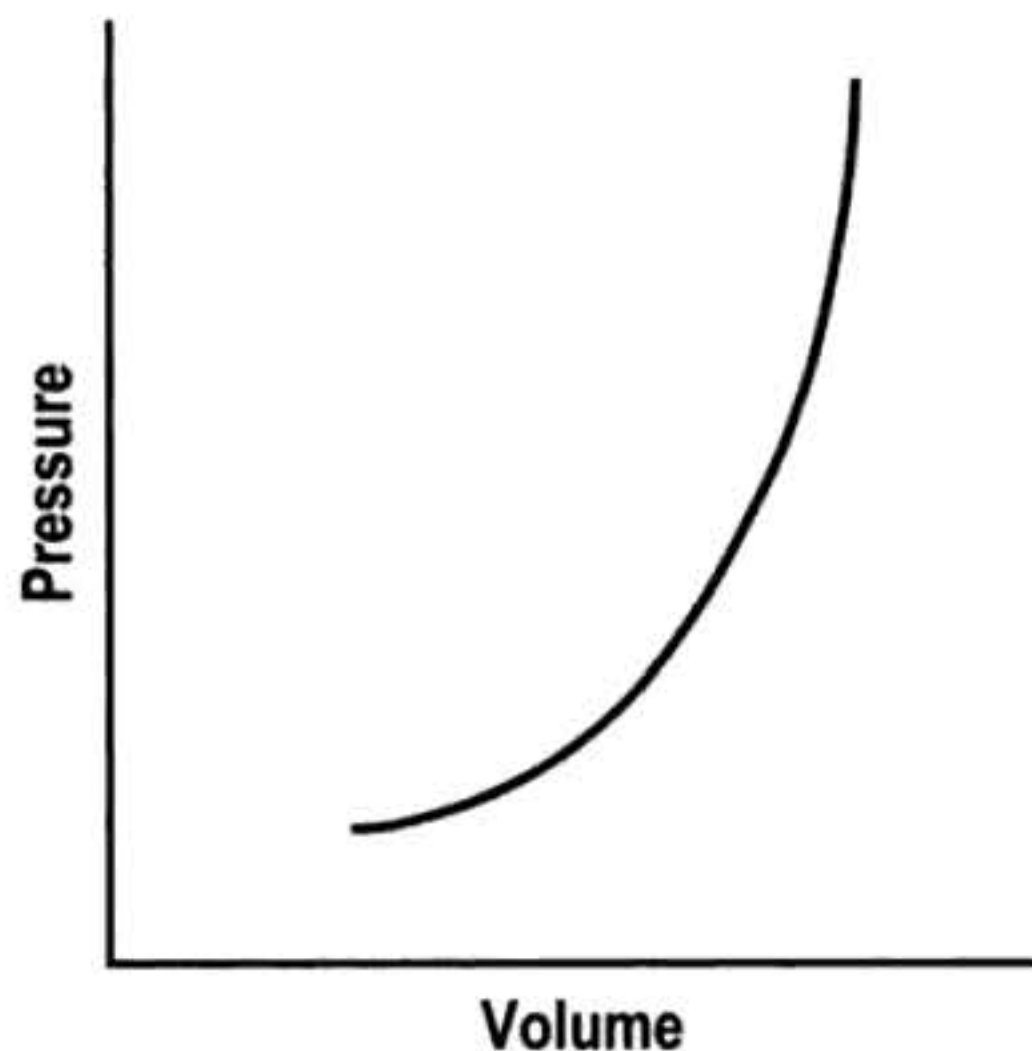


Fig. 5.2. Typical pressure/volume curve for the intracranial compartment (Courtesy of Anton Hoffman-reprinted with permission¹).

breathing, cardiovascular status). In doing so, the brain will benefit as well as the rest of the patient. Quick assessment tests (QATs), including packed cell volume (PCV), total solids (TS), azostix (AZO), and blood glucose (BG), are part of the initial patient assessment. Since hypovolemia and hypoxemia are strongly correlated with elevated ICP and increased mortality in human head-trauma victims, they need to be addressed immediately.

A. Fluid therapy

There is often concern that aggressive intravenous fluid therapy to counteract hypotension in the brain-injured patient may aggravate brain edema. There is both evidence to support and evidence to refute this concern. Because of this concern, there have been recommendations to volume-limit victims of severe head trauma. Such recommendations are not only unfounded, but *strictly contraindicated*. There is no debate over the disastrous consequences to the injured brain if hypotension is allowed to persist. Hypotension has been repeatedly shown to be a reliable predictor of sustained elevations of ICP and increased mortality in human head-trauma victims. Blood pressure must be restored to normal levels as soon as possible. A patient with a systolic blood pressure less than 90 mmHg is to be considered hypotensive. Some volume replacement fluids (hetastarch, hypertonic saline) afford some protection to the edematous brain, even if used with large volumes of crystalloids (LRS, 0.9% NaCl). Hetastarch and hypertonic saline can improve MABP and thus CPP without exacerbating brain edema. If the patient is anemic, whole-blood transfusion may assist in maintaining normovolemia as well as adequate tissue oxygenation. Fluid support may include one or more of the following choices:

1. Hetastarch: 10–20 ml/kg to effect (up to 40 ml/kg/hr) for shock. This can be given as a rapid bolus in dogs; give it in 5 ml/kg increments over 5–10 min in cats. Hetastarch is the author's fluid of choice in restoring normal blood pressure in the head-trauma victim.
2. Hypertonic saline (7%): 4–5 ml/kg over 3–5 min for shock. Although hypertonic saline has been shown to improve MABP and CPP and protect against increased ICP, sodium has recently been implicated as the major osmotic agent contributing to brain edema. Hypertonic saline may have a global protective effect on the brain, but theoretically may lead to increased compromise to focal areas of damaged parenchyma.
3. Dextran 70: 10–20 ml/kg (up to 40–50 ml/kg/hr) for shock in dogs. Cats should be administered dextran 70 as 5 ml/kg boluses, given over 5 to 10 min, with a maximum of 20 ml/kg. Dextran 70, given as a sole fluid support, has not exhibited the beneficial effects demonstrated with hetastarch and hypertonic saline. Therefore, dextran 70 should be considered as a potential adjunctive fluid therapy choice.
4. Crystalloids (LRS, 0.9% saline): 90 ml/kg/hr (dogs), 60 ml/kg/hr (cats) for shock. Since overhydration with subsequent worsening of brain edema and increased ICP is a concern with crystalloid administration, the "shock dose"

of crystalloids should be given to effect. If the entire volume is not necessary to restore euvolemia and normal MABP, fluid administration should be tapered when these physiologic goals are met.

5. Blood products: 4–10 ml/kg/hr (typically over 4 to 6 hr) in the stable patient, faster (to effect) if the patient is unstable. Goals of therapy with blood products are a packed cell volume (PCV) between 25% and 30%, and a plasma albumin level over 2.0 g/dl.

B. Oxygenation and hyperventilation

Hyperoxygenation is recommended for most acutely brain-injured animals. Oxygenation status of a head-trauma victim can be initially assessed based upon breathing rate and pattern, mucous membrane and tongue color, and thoracic auscultation. Pneumothorax and pulmonary contusions are common sequelae of trauma, and need to be addressed, if present. If arterial blood gas analysis is available, the partial pressure of oxygen in arterial blood (PaO_2) should be maintained at or above 90 mm Hg for dogs, and 100 mm Hg for cats. Pulse oximeters are extremely useful, and relatively accurate estimators of oxygenation status. However, the reliability of pulse oximeters varies with model used and with the PaO_2 level (pulse oximeters may overestimate oxygenation status at lower PaO_2 levels). In general, oxyhemoglobin saturation values (SaO_2) from pulse oximeters should be interpreted as shown in Table 5.1.

Patients who are conscious and not obviously deteriorating neurologically should be administered supplemental oxygen via face mask, nasal oxygen catheter, or transtracheal oxygen catheter. Face masks tend to stress dogs and cats, and should only be used temporarily, until another form of oxygen (O_2) delivery can be instituted (e.g., nasal O_2). The use of an O_2 cage is generally an ineffective method of administering supplemental O_2 to the severely brain-injured patient, as most of these patients require frequent or constant monitoring. Oxygen cages do not allow for concomitant close patient observation (requires opening the cage door) and maintenance of a high-oxygen environment. With nasal (Fig. 5.3) and transtracheal O_2 catheters, an inspired oxygen concentration of 40% is provided with flow rates of 100 ml/kg/min and 50 ml/kg/min, respectively. Oxygen concentrations as high as 95% can be delivered with proportionally higher flow rates. Nasal O_2 catheters must not be placed farther than the level of the medial canthus (to avoid entering the cranial vault through a fracture site), and inadvertent jugular vein compression should be avoided while placing a transtracheal O_2 catheter. Patients who are losing or have lost consciousness should be intubated and venti-

Table 5.1: Interpretation of Pulse Oximeter SaO_2 Values

SaO_2	PaO_2	Interpretation
>95%	>80%	Normal
<89%	<60%	Serious hypoxemia
<75%	<40%	Lethal hypoxemia



Fig. 5.3. Nasal oxygen administration in a head-traumatized cat (Reprinted with permission¹²).

lated. In the patient with oscillating levels of consciousness, a tracheostomy tube may be indicated for assisted ventilation. Arterial blood gas measurement is the best way to monitor PaCO_2 levels. End-tidal CO_2 measurement is a useful monitoring tool, but tends to underestimate the true PaCO_2 levels. Ventilatory rates of 10–20 breaths per minute should keep PaCO_2 levels between 25 and 35 mm Hg. While this has been the recommended range of PaCO_2 levels to prevent excessive brain vasodilation, recent evidence suggests the PaCO_2 less than 30 mm Hg may lead to excessive vasoconstriction with subsequent impairment of CPP. Hyperventilation may be deleterious to patients whose ICP elevation is not due to hypercarbia-induced dilation of brain vasculature. Indiscriminate use of hyperventilation to decrease ICP should be avoided, as excessive vasoconstriction of brain vasculature can decrease CPP.

IV. Secondary Assessment and Diagnostic Procedures^{1,3,14,15,23}

Once normovolemia and appropriate oxygenation/ventilation are attained, the patient should be more carefully assessed for other injuries to the nervous system (e.g., vertebral fractures/luxations), as well as to other body systems (lungs, abdominal organs, musculoskeletal system). A complete neurologic examination should be performed at this time. Specific medical therapy for brain injury should begin coincident with the secondary assessment. Additional bloodwork as well as radiographs may be warranted. Imaging of the patient's head is often indicated, especially in those animals that fail to respond to aggressive medical therapy, or deteriorate after



Fig. 5.4. Depressed skull fracture in a dog with deteriorating neurologic status following severe head trauma (Reprinted with permission¹²).

responding to such therapy. Skull radiographs are unlikely to reveal clinically useful information in cases of severe head trauma, but on occasion may reveal evidence of depressed fractures of the calvaria (Fig. 5.4). Computed tomography (CT) is the preferred modality for imaging the head in cases of severe brain injury. CT is preferred over magnetic resonance (MR) imaging in head-trauma cases for several reasons. CT images are obtained much more quickly than MR images (an important advantage in the critical patient scenario), and acute hemorrhage and bone are better visualized with CT than with MR imaging (Fig. 5.5).

V. Specific Medical Therapy for the Head-Trauma Victim^{1,4,8,10,12-15,23-33}

A number of medical therapies have been recommended for the head-trauma victim, most of which are controversial and not definitively proven to affect outcome. In



Fig. 5.5. Noncontrast, computed tomographic (CT) brain image of a brain-injured dog. Note the evidence of intraparenchymal hemorrhage (Reprinted with permission¹).

addition to these treatments, proper physical therapy and nutritional support are vital to a positive outcome. In the recumbent patient, the head should be kept slightly elevated (15° – 30°) to assist in lowering ICP.

A. Mannitol (20%–25%)

Mannitol is an osmotic diuretic that has demonstrated efficacy in reducing brain edema and ICP in cases of severe brain injury. There are multiple proposed mechanisms of actions by which mannitol decreases ICP, including reflex vasoconstriction of brain vasculature via decreasing blood viscosity, reduction of cerebrospinal fluid (CSF) production, scavenging free-radical species, and osmotically drawing extravascular edema fluid into the intravascular space. The mechanism thought to be primarily responsible for mannitol's most immediate and profound effects on ICP is reflex vasoconstriction. This response of the brain vasculature to the decreased blood viscosity caused by an intravenous mannitol bolus is linked to the brain's pressure autoregulation mechanism; it allows for improved CPP at a lower brain-blood volume (decreased ICP). The effect of reflex vasoconstriction on ICP occurs within a few minutes, whereas the osmotic action has an effect within 15–30 min. Mannitol's effect on decreasing brain edema lasts between 2 and 5 hours.

Mannitol is administered intravenously over 10–20 min at a dosage of 0.5–1.0 g/kg. Serum osmolality and electrolytes should be monitored with repeated mannitol use; osmolality should be maintained at or below 320 mOsm/L (to prevent renal failure) and electrolytes should be kept within normal limits. Serum osmolality can be approximated by multiplying the patient's Na^+ value by a factor of 2. A useful guideline to prevent unwanted side effects of mannitol use is to limit administration of mannitol to three boluses in a 24-hr period. Since mannitol tends to crystallize at room temperature, it should be warmed to approximately 37°C (99°F) and administered through an in-line filter. Administration of furosemide (2–5 mg/kg) a few minutes before mannitol administration may be synergistic in reducing ICP. A frequently raised theoretical concern about mannitol administration is the possibility of exacerbating ongoing brain hemorrhage due to mannitol's osmotic action. This concern is unfounded clinically and should be ignored. Another concern about mannitol use in the head-trauma victim involves the concept of "reverse osmotic shift"; with prolonged contact time (multiple doses or continuous infusions), the extravascular concentration of mannitol in the brain can accumulate and exceed the intravascular concentration. The result of this phenomenon is increased brain edema. With appropriate use of mannitol, "reverse osmotic shift" is extremely unlikely to occur. In general, once the head-trauma victim is hemodynamically stable, mannitol should be considered first-line therapy for decreasing ICP and improving CPP.

B. Glucocorticoids

Despite their traditional role in the treatment of CNS trauma, there is little evidence to support the use of glucocorticoids in victims of severe head trauma. "Standard" dosing protocols of prednisone and dexamethasone are particularly

unlikely to benefit brain-injured patients. Limited evidence of efficacy exists for the “high-dose methylprednisolone” protocol in severe head trauma. This protocol involves the intravenous administration of a 30-mg/kg bolus of methylprednisolone sodium succinate (Solu-Medrol) at time 0, and 15 mg/kg boluses at 2 hr and 6 hr. These boluses should be given over several minutes. A continuous intravenous infusion of 2.5 mg/kg/hr may then be instituted, dependent on the patient’s response. The “high-dose” protocol is suspected to provide therapeutic benefit via free-radical scavenging action, rather than by activation of steroid receptors. Lazaroids, or 21-aminosteroids, are analogs of methylprednisolone that do not activate glucocorticoid receptors. These agents will hopefully provide therapeutically beneficial free-radical scavenging activity without producing undesirable steroid receptor-mediated side effects. Because large doses of glucocorticoids can exacerbate hyperglycemia, the patient’s blood glucose should be checked before administering the “high-dose” protocol. Hyperglycemia (over 200 mg/dl) has been associated with increased mortality in severely head-injured people. In a recent study, the degree of hyperglycemia was found to be correlated with severity of neurologic dysfunction in brain-injured dogs and cats; however, an association between level of hyperglycemia and outcome was not found. It is postulated that the provision of extra glucose to the ischemic brain helps to fuel anaerobic glycolysis, with resultant increases in brain lactic acid. The increased lactic acid levels cause further brain damage. There is insufficient evidence to support glucocorticoid use as a standard therapy for head-trauma victims. “High-dose” methylprednisolone therapy should be considered as adjunctive treatment in those patients not responding adequately to appropriate resuscitative (fluid and oxygen therapy) measures and mannitol administration who are not hyperglycemic.

C. Miscellaneous therapies

In addition to lazaroids, a number of free-radical scavenging agents have been investigated for potential use in victims of severe head injury. Some examples include dimethylsulfoxide (DMSO), allopurinol, deferoxamine mesylate, and liposome-encapsulated forms of superoxide dismutase and catalase. Despite experimental evidence of efficacy for these drugs, clinical evidence to support the use of these agents in the head-trauma victim is currently lacking. Similarly, there exists some experimental, yet not clinical, evidence of efficacy for antagonists of opiate and glutamate receptors, as well as several calcium channel blockers. Induction of a barbiturate coma with pentobarbital has been advocated as a “last ditch” effort to decrease metabolic demands of the injured brain, thereby mitigating effects of ischemia and decreasing ICP. In addition to limited evidence of clinical efficacy, induction of a barbiturate coma in a brain-injured patient may be detrimental to survival. Barbiturates may lead to hypotension and/or hypoventilation, both of which will cause increased ICP. Recent experimental and clinical evidence in human head-injured patients supports the induction of moderate hypothermia (32°–34°C, 89.6°–93.2°F) as a means to decrease ICP and improve outcome. Although traditionally thought to decrease ICP via decreasing brain

metabolic demands, induced hypothermia is now thought to provide beneficial results mainly by inhibiting release of inflammatory cytokines and glutamate.

VI. Indications for Surgery^{1,4,8,12,15,34-39}

In general, indications for surgical intervention are clearly defined in human head-trauma management. The guidelines for when to pursue surgery in brain-injured people center on the presence and extent of intracranial hemorrhage. Measurements of focal hemorrhage and accompanying midline shifts of the falx cerebri from CT images are combined with ICP measurements in making surgical decisions in people with severe head trauma. Surgical intervention has traditionally played a relatively minor role in canine and feline head-trauma management, due to the belief that clinically significant intracranial hemorrhage is rare in these species. There is some evidence that brain-injured dogs and cats may experience surgically manageable intracranial hemorrhage, similar to people (Fig. 5.6). With the increased availability of CT facilities for dogs and cats, surgery may begin to play a larger role in canine and feline head-trauma management. Other potential indications for surgery in the brain-injured dog or cat include open skull fractures, depressed skull fractures (with associated neurologic impairment), and retrieval of potentially contaminated bone fragments or foreign material lodged in brain parenchyma (Fig. 5.7). While surgical removal of focal intracranial hemorrhage is an accepted and proven aspect of human head-trauma management, there is debate in the literature concerning the value of craniotomy solely as a decompressive maneuver in the patient deteriorating neurologically despite aggressive medical therapy (i.e., with no evidence of focal intracranial hemorrhage). The value of craniotomy solely as a decompressive surgery is unknown in canine and feline head trauma. It has been recently demonstrated, however, that in normal dogs and cats, combined craniotomy/durotomy results in dramatic decreases in ICP. Surgical intervention should be strongly considered in head-traumatized dogs and cats that are deteriorating neurologically despite aggressive medical therapy.

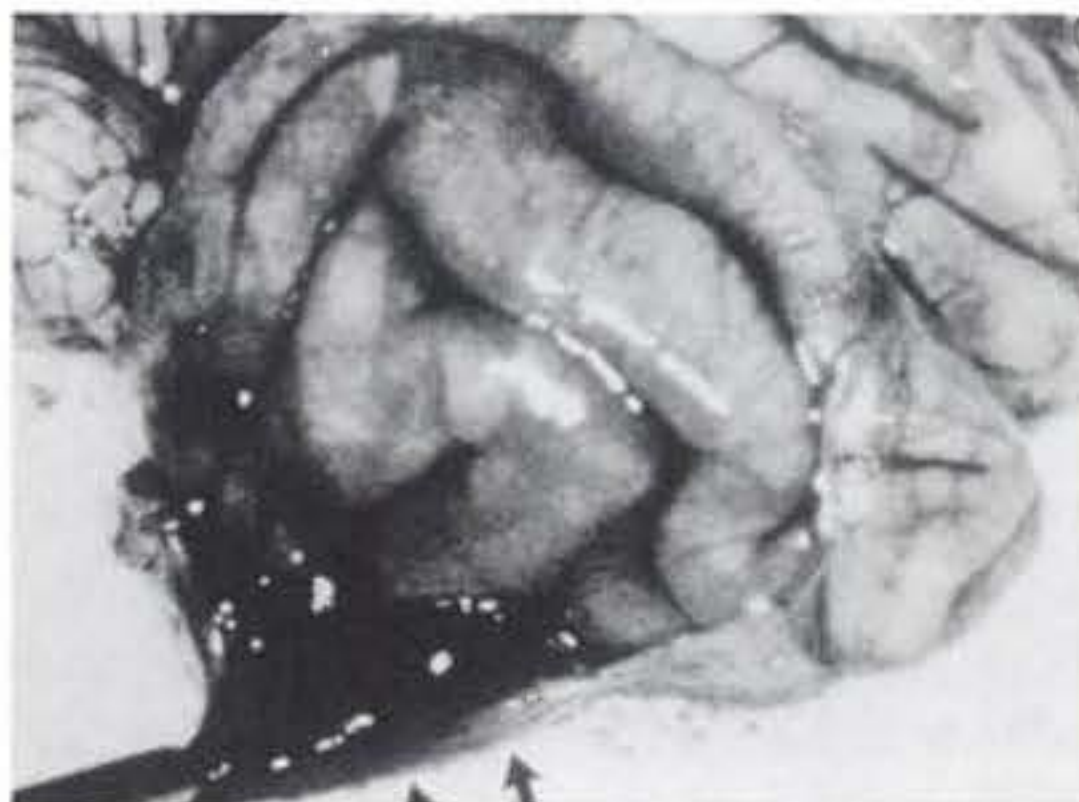


Fig. 5.6. Large subdural hematoma in a cat that died following severe head trauma (Reprinted with permission¹²).

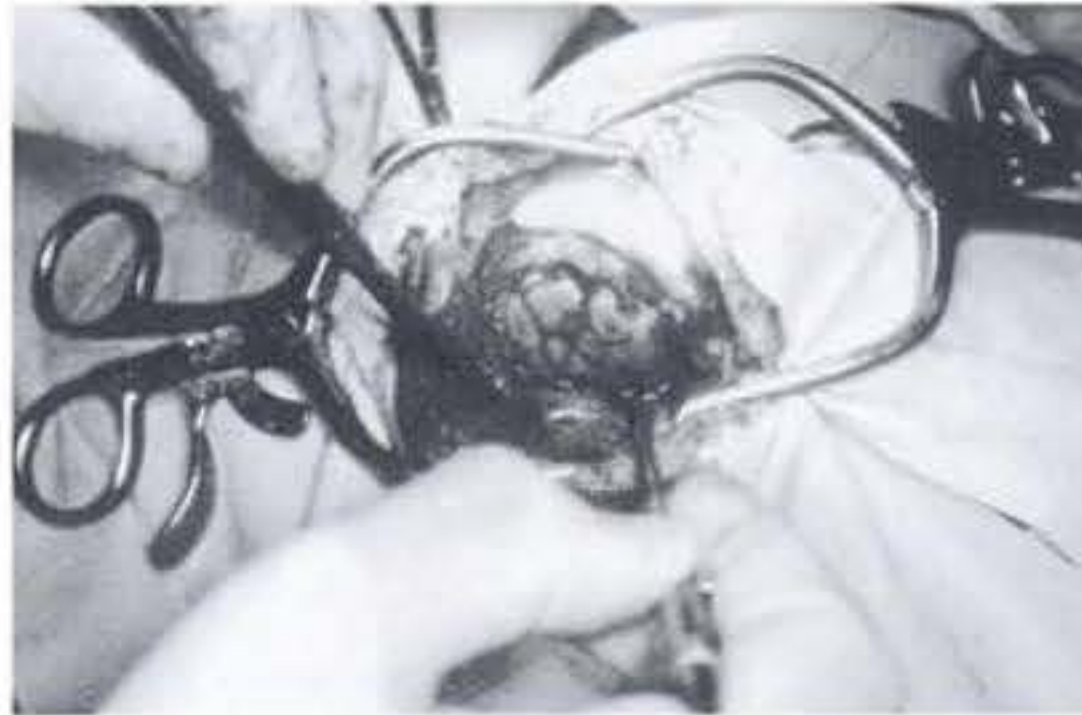


Fig. 5.7. Decompressive craniotomy in a dog. The patient had a large bone fragment lodged in the cerebral parenchyma and a midline shift evident on CT imaging (Reprinted with permission¹²).

VII. Intracranial Pressure (ICP) Monitoring^{1,4,7,8,12,14,15,24,38-44}

Medical and surgical decisions based upon ICP measurements, rather than on gross neurologic findings, have decreased morbidity and mortality in human head-trauma victims. In general, recommendations for human head-trauma victims are to maintain ICP below 20 mm Hg and CPP at a minimum of 70 mm Hg. Prognostic information can also be obtained from ICP measurements. ICP monitoring is a standard procedure for human head-trauma management, but has only recently been investigated in dogs and cats. A fiberoptic ICP monitoring device has been shown to be both technically easy to place and reliable in dogs and cats. With this monitor, ICP can be measured directly from brain parenchyma. The extremely high cost of the fiberoptic system will likely limit its use in veterinary medicine. An inexpensive, easily implantable, epidural ICP monitoring system has recently been evaluated in normal cats; this system was found to be comparable in accuracy to the fiberoptic ICP system.

VIII. Prognosis and Complications^{1,12,45-47}

The overall prognosis for victims of severe head trauma is considered guarded to poor. However, the recuperative ability of brain-injured dogs and cats is tremendous, and aggressive therapy may be successful in many apparently hopeless cases. Predicting the outcome of an individual patient is difficult, but several factors may assist the clinician in estimating prognosis. These factors include level of consciousness, presence or absence of brain-stem reflexes, age and general physical status, and presence and extent of other concurrent injuries. A dog or cat that is comatose with absent brain-stem reflexes from the time of impact is generally less likely to recover than a patient who is obtunded with intact brain-stem function. Potential complications associated with brain-injured patients include coagulopathies (e.g., disseminated intravascular coagulation-DIC), pneumonia, fluid/electrolyte abnormalities (e.g.,

central diabetes insipidus), and sepsis. Seizure activity may develop around the time of trauma (suggesting intraparenchymal hemorrhage) or months to years after trauma (development of a glial “scar”-seizure focus). Most of these complications are treatable and/or preventable.

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Chapter 6

SEIZURES AND NARCOLEPSY

William B. Thomas

SEIZURES

I. Introduction

Seizures are the most common neurologic problem in small-animal medicine. Clients are often emotionally distraught because of the violent, unpredictable nature of seizures. An accurate diagnosis is the first step in management. The underlying cause of the seizures is identified and treated if possible. In the case of idiopathic epilepsy, there is no cure and management usually entails daily administration of medication. Optimal management of this syndrome depends on the veterinarian and client working together as a team, with the client actively participating in decisions. With proper treatment, the patient and client can usually maintain a good quality of life.

II. Pathophysiology¹⁻³

An epileptic seizure is the clinical manifestation of excessive and/or hypersynchronous electrical activity in the cerebral cortex. Brain neurons are inherently excitable. Defects that alter the excitability of a group of neurons can lead to marked and prolonged depolarization, called a paroxysmal depolarizing shift (PDS). This shift can involve neurons in a specific region of the brain (leading to a focal seizure) or involve the entire cerebrum (leading to a generalized seizure). Excessive depolarization can also spread from a focal hyperexcitable area (seizure focus) and induce other areas of the brain to seizure. Although the precise mechanisms involved are incompletely understood, theories include:

- A. Inadequate neuronal inhibition—major inhibitory neurotransmitters include gamma aminobutyric acid (GABA) and glycine.
- B. Excessive neuronal excitation—major excitatory neurotransmitters include aspartate and glutamate.
- C. A combination of A and B.

III. Types of Seizures³⁻¹⁵

A. Generalized seizures

These are seizures in which the initial clinical signs reflect involvement of both cerebral hemispheres. Generalized tonic-clonic seizures, formerly called grand mal seizures, are the most common type of seizures in dogs and cats.

1. Generalized tonic-clonic seizures

The first part of the seizure is the tonic phase, during which there is sustained contraction of all muscles. The animal typically loses consciousness and falls to its side in opisthotonus with the limbs extended. Breathing is often irregular or absent and cyanosis is common. The patient often salivates, urinates, or defecates. The tonic phase lasts for a minute or so and then gives way to the clonic phase, during which there is paddling or jerking of the limbs and chewing movements. The clonic phase lasts a variable period of time but usually no more than several minutes. Some animals suffer milder generalized tonic-clonic seizures in which consciousness is maintained.

2. Tonic seizures

During a tonic seizure, the abnormal motor activity consists only of generalized muscle rigidity without a clonic phase.

3. Clonic seizures

These seizures consist of paddling and jerking with no tonic component.

4. Atonic seizures

These rare seizures are manifested as sudden, often brief losses of muscle tone.

5. Myoclonic seizures

These are characterized by brief, shocklike contractions that may be generalized or confined to individual muscle groups. There are other causes of myoclonic jerks; not all myoclonic jerks are seizures.

6. Absence seizures

Generalized absence seizures in people are defined as abrupt, brief losses of consciousness associated with a specific pattern on electroencephalography (EEG). These were formerly called petit-mal seizures; although this term is often used erroneously to refer to any sort of mild seizure. True absence seizures are rarely recognized in veterinary medicine.

B. Focal (partial) seizures

Focal seizures are those in which the initial clinical signs indicate abnormal neuronal activity in one region of a cerebral hemisphere. *Simple focal seizures* are those in which consciousness is not impaired. *Complex focal seizures* involve some alteration of consciousness. Any portion of the body may be involved during a focal seizure depending on the region of the brain affected. There may be asymmetric motor or sensory signs. Examples include rhythmic contractions of facial or masticatory muscles, licking or chewing at a region of the body, and "fly-biting" seizures. Fly-biting seizures have been observed in many breeds of dogs, most notably Cavalier King Charles spaniels. Focal seizures can cause autonomic signs, such as hypersalivation (ptyalism), vomiting, diarrhea, and apparent abdominal pain. Complex focal seizures may be manifested as impaired consciousness and bizarre behavior, such as unprovoked aggression (canine rage syndrome or episodic dyscontrol) or extreme, irrational fear (psychic or psychomotor seizures). In

some cases, it is difficult to discriminate between a focal seizure and other types of episodes, such as syncope, narcolepsy, and behavioral disorders.

Occasionally, animals will display episodic involuntary movements of a body part without an alteration of consciousness. English bulldogs and Boxer dogs tend to display rhythmic side-to-side wobbling of the head (a “no” movement), whereas Doberman Pinscher dogs tend to have an up-and-down motion (a “yes” movement). Other dogs have been reported with repetitive limb movements. These disorders may represent simple focal seizures, but are similar to human dyskinesias. Dyskinesias are involuntary movements due to abnormalities of the basal nuclei. Episodic muscle hypertonicity (see Chapter 13) may also represent a dyskinesia. Definitive diagnosis of focal seizure activity is sometimes based on EEG or response to antiseizure drugs. Focal seizures may have secondary generalization. A seizure may start in a focal region only to spread throughout both cerebral hemispheres culminating in a generalized seizure. The secondary spread can occur so rapidly that the initial focal component is missed.

IV. Stages of a Seizure^{1,5,7}

A. Prodrome

A prodrome is a long-term indication of a forthcoming seizure. The patient may exhibit abnormal behavior, such as restlessness and uncontrolled vocalizing, during the hours to days before a seizure. Prodromes are not always recognized.

B. Aura

An aura is the initial sensation of a seizure before there are observable signs. Auras usually last seconds to minutes and are caused by the initial abnormal electrical activity in the brain. In other words, the aura is the start of a seizure. Affected animals may hide, seek their owners, seem agitated, or vomit just before a seizure. The difference between a prodrome and an aura is that prodromes are long lasting and not associated with abnormal EEG activity, while auras are short lasting and caused by abnormal electrical activity.

C. Ictus

The ictus is the seizure itself.

D. Postictal stage

Postictal signs are transient clinical abnormalities in brain function that are caused by the ictus and appear when the ictus has ended. These may include disorientation, restlessness, ataxia, blindness, and deafness. Postictal abnormalities usually resolve after several minutes, but can last for days, especially after prolonged seizures.

V. Epilepsy^{1,4,5}

- A. Epilepsy is a condition characterized by recurrent seizures over a long period of time. Epilepsy is not a specific disease; it is a clinical sign.
- B. Provoked seizures, also called reactive seizures, are seizures that occur at the time of a systemic disorder or brain insult. If the seizures stop when the underlying condition resolves, the patient does not have epilepsy because the condition is not chronic. Seizure activity caused by acute toxicity is an example.
- C. Idiopathic epilepsy, also called primary epilepsy, refers to recurrent seizures in which there is no identifiable brain abnormality other than seizures.
- D. Symptomatic epilepsy, also called secondary epilepsy, is recurrent seizures that are caused by an identifiable lesion or other specific etiology.

E. Causes of symptomatic epilepsy

Seizures can be caused by a primary lesion of the brain (intracranial disorders) or by a process outside the brain that affects the brain (extracranial disorders).

1. Intracranial

Intracranial disorders that may lead to seizure activity include degenerative diseases (e.g., storage diseases), hydrocephalus, neoplasia, infectious/inflammatory disease (e.g., GME), trauma, and ischemic/vascular disorders.

2. Extracranial

Extracranial disorders that may lead to seizures include hepatic encephalopathy, hypoglycemia, electrolyte imbalances (e.g., hypocalcemia), and toxins (e.g., lead, ethylene glycol).

In general, young animals are prone to infectious diseases, developmental disorders, and storage diseases. Young animals also are more likely to ingest toxins, such as lead. Older animals are at increased risk of neoplasia and vascular disorders. Extracranial causes are usually identified by laboratory analysis and historical evidence of toxin exposure. Diagnosis of intracranial disorders usually entails brain imaging and analysis of cerebrospinal fluid.

VI. Idiopathic epilepsy^{1,4,7,16-23}

This is the most common cause of seizures in dogs. Most cats with seizures have an underlying identifiable cause, although idiopathic epilepsy does occur in cats. There are several consistent features of idiopathic epilepsy in dogs:

- A. The age of onset is usually 1–5 yr of age.
- B. Idiopathic epilepsy is inherited in some breeds, including the Beagle, Belgian terrier, Keeshound, Dachshund, British Alsatian, Labrador retriever, Golden retriever, and Collie, but it can occur in any breed of dog or cat.

- C. Generalized tonic-clonic seizures are the most common type of seizure, but other types of generalized or focal seizures can occur.
- D. Seizures usually occur spontaneously and are more common at night or when the patient is resting or sleeping.
- E. Initially, seizures are usually infrequent (every 4 wk or so) but without therapy, or with inadequate therapy, seizures tend to increase in frequency.

VII. Diagnostic Evaluation^{1,24,25}

A. Differential diagnosis

The diagnostic evaluation is designed to determine if the patient is having seizures, and, if so, the cause of the seizures. Seizures are recognized by their spontaneous onset, stereotypic signs, self-limiting time course and exclusion of common imitators. Idiopathic epilepsy is a clinical diagnosis based on the typical age of onset, lack of interictal abnormalities, and exclusion of other causes. Symptomatic epilepsy should be suspected when seizures start before 1 yr or after 5 yr of age, the patient suffers focal seizures, there is a sudden onset of multiple seizures, or there are interictal abnormalities detected on history, examination, or laboratory tests. Several disorders can be mistaken for seizures:

1. Syncope is characterized by partial or complete loss of consciousness, lack of violent motor activity, short duration and lack of postictal signs. It is often associated with exercise and caused by cardiac or respiratory disease.
2. Narcolepsy is usually manifested as episodes of flaccid paralysis or loss of consciousness precipitated by excitement.
3. Myasthenia gravis can cause stiffness, tremor, or weakness with normal consciousness. Clinical signs of myasthenia gravis may be induced by exercise. Some myopathies can cause similar clinical signs.
4. Peripheral vestibular dysfunction is characterized by ataxia, head tilt, and abnormal nystagmus with no impairment of consciousness.
5. Episodes of encephalopathy can cause disorientation, ataxia, blindness, and abnormal behavior. Hepatic encephalopathy is an example.
6. Normal or abnormal movements during sleep consist of twitching, paddling, or vocalizing while the patient is asleep. Waking the animal can interrupt these and there are no postictal signs.
7. Behavior disorders, such as stereotypy, can cause specific patterns of bizarre behavior. These episodes can usually be interrupted and there are no postictal signs.
8. Pain, especially neck pain, can cause episodes of muscle rigidity or stiffness and crying. Consciousness is not impaired.

B. History

1. A detailed and accurate history is the cornerstone of diagnosis. A description of the seizures should be elicited from the client, including their frequency and duration, and any focal signs at the start of the seizure, such as turning the head to one side or jerking of one limb. In some cases it helps if the client videotapes the episodes.
2. The client should be asked if the events occur at a certain time of day or in association with situations such as feeding or exercise.
3. Inquiries should also be made concerning any known or suspected familial history of seizures, significant injuries or illnesses, vaccination status, diet, and potential exposure to toxins. Clients should be asked whether or not any interictal abnormalities, such as changes in behavior, gait, appetite, weight, or sleep habits have been observed.

C. Examination

A thorough physical examination is important to detect signs of systemic illness that might suggest an underlying cause for the seizures. The clinician should perform a complete neurologic examination to detect any persistent neurologic deficits. Cerebral lesions often cause focal, relatively subtle deficits such as delayed proprioceptive positioning on one side or blindness in one visual field. Caution is advised when interpreting the neurologic examination shortly after a seizure because of the possibility of temporary postictal deficits. Repeating the examination at a later time may be necessary to determine if any deficits persist.

D. Laboratory evaluation

1. A complete blood count and serum chemistry profile are indicated to screen for metabolic causes of seizures.
2. Serum bile acids are tested in young animals to identify porto-systemic shunts.
3. Blood lead determination should be performed in patients with possible exposure to lead, patients from areas with a high incidence of lead poisoning, and in animals less than 1 yr of age.
4. Thyroid function is evaluated in adult dogs because of possible links between hypothyroidism and seizures and the effects of phenobarbital on thyroid testing.

E. Ancillary diagnostic testing

Cerebrospinal fluid analysis and computed tomography or magnetic resonance imaging are indicated in dogs with interictal neurologic deficits, focal seizures, seizures refractory to drug therapy, or an onset of seizures at less than 1 yr or greater than 5 yr of age. These tests are also indicated in any cat with seizures because idiopathic epilepsy is less common in this species. Electroencephalography may be helpful in confirming epileptic activity when the veterinarian is unsure whether the events are seizures or nonepileptic episodes.

VIII. General Aspects of Treatment

The goal of therapy is to reduce the frequency and severity of the seizures to a level that does not substantially compromise the quality of life for the pet and family while avoiding serious side effects.

Patients with a single seizure, provoked seizures, or isolated seizures separated by long periods of time generally do not require treatment. Treatment is indicated for patients with any episode of unprovoked status epilepticus, multiple seizures in a short period of time, or an underlying, progressive disorder responsible for the seizures. Patients treated early in the course of epilepsy may have better long-term control of their seizures compared to those that have multiple seizures before treatment is started. The client needs to understand the goals of therapy, potential side effects, and cost and effort associated with treatment and monitoring. They should appreciate the importance of regular administration of medication, and need to know what to do if a dose is missed (in general, the missed dose is given as soon as the mistake is recognized, then the next dose is given on schedule). Having the client keep a log of the time, date, and characteristics of each seizure and any side effects helps assess therapeutic efficacy. Because of the variability in pharmacokinetics among patients, initial dose recommendations are a general guide only. Because of sensitivity to side effects and lack of prior metabolic induction, most new patients are started at the lower end of the dose range. Autoinduction of metabolism will often require an increase in dose in the weeks to months after starting therapy. On the other hand, patients with frequent or severe seizures are often best managed by starting at the higher end of the dose range or using a loading dose. Once the seizures are controlled, the dose may need to be adjusted downward to minimize side effects. Any drug used should be given an adequate chance to work and should not be discarded prematurely. Antiseizure drugs often must be administered for several weeks or longer before obtaining maximum effects. Furthermore, it may take several months or more to adequately evaluate seizure control in a patient that has seizures separated by long periods of time. A common cause of poor seizure control is failure to maximize the dose before discarding a particular drug. This may lead to the need to backtrack at a later date for a second, more aggressive trial. This can be difficult, however, because once a client is convinced a particular drug is ineffective, they are often reluctant to agree to a second trial. Therapeutic monitoring of serum drug concentrations can be helpful in determining the optimal dose. Indications for therapeutic monitoring include:

- A. When steady-state blood levels are reached after starting treatment, changing dose, or immediately after a loading dose.
- B. When seizures are not controlled despite an apparently adequate dose. This helps determine the need for dose adjustment before the drug is changed or a second drug is added.

- C. When signs of dose-related toxicity occur.
- D. Every 6 to 12 mo to verify that changes in pharmacokinetics have not caused blood concentrations to drift out of the intended range.

IX. First-Line Antiseizure Drugs

A. Phenobarbital^{1,24-34}

1. One of two first-choice drugs for dogs, phenobarbital is the initial drug-of-choice for cats. Proposed mechanisms of actions for phenobarbital include increasing neuronal responsiveness to GABA, antiglutamate effects, and decreasing calcium flow into neurons. Phenobarbital is metabolized primarily by the liver.
2. The elimination half-life is 40–90 hr. Ten to 15 days are required to reach steady-state kinetics.
3. The initial dose is 2–5 mg/kg orally, every 12 hr in dogs; 2.5 mg/kg orally, every 12 hr in cats. After that, the dose is tailored to the individual patient based on seizure control, side effects, and therapeutic monitoring.
4. Serum levels should be checked 2–3 wk after initiating therapy or changing the dose. The therapeutic range is 20–35 $\mu\text{g/ml}$ (85–150 $\mu\text{mol/l}$). Traditionally, it has been recommended to obtain a trough sample immediately before a dose is due. Recently, however, it has been shown that there is no significant impact of the timing of blood collection (i.e., “trough” versus “peak” level) on the serum phenobarbital level measured in the vast majority of dogs (91%) evaluated. Serum separator tubes should be avoided because the silicone will bind phenobarbital.
5. Sedation, ataxia, polyuria/polydipsia, and polyphagia are common dose-dependent side effects. Sedation and ataxia often improve after several weeks of therapy. Blood dyscrasia is a rare, possibly idiosyncratic adverse effect.
6. Elevation of liver enzymes, especially alkaline phosphatase, is common. This does not necessarily indicate clinically significant liver disease or the need to stop therapy. The risk of liver toxicity appears to be greater with blood concentrations higher than 35 $\mu\text{g/ml}$ or when multiple, potentially hepatotoxic drugs are used. Bile acids are a better test for hepatotoxicity and are checked every 6–12 mo to screen for liver disease, which is reversible if detected early and the drug is stopped.
7. Phenobarbital decreases thyroxine (T₄) and free thyroxine (fT₄), and increases thyroid-stimulating hormone (TSH) in dogs, without inducing clinical signs of hypothyroidism.

B. Bromide^{1,35-41}

1. Bromide is one of the initial drugs-of-choice for dogs. It is also added to phenobarbital when the seizures are not adequately controlled despite serum phe-

nobarbital levels of 20–35 $\mu\text{g/ml}$. The bromide ion is believed to hyperpolarize neuronal membranes after traversing neuronal chloride channels. Bromide is renally excreted and is the preferred antiseizure drug for patients with liver disease.

2. Bromide may be effective in cats; however, it has been associated frequently with reversible pneumonitis (bronchial asthma) in this species.
3. Bromide is administered as potassium bromide or sodium bromide in solution or capsules. Use of the solution is typically less expensive and makes it easier to adjust the dose. There is no difference in efficacy for the potassium or sodium salt, although potassium bromide is preferred when sodium intake must be restricted (for example, congestive heart failure). Sodium bromide is preferred when potassium intake must be restricted (for example, hypoadrenocorticism). Bromide is not manufactured for medical use in North America, but can be compounded by many pharmacists.
4. The elimination half-life is 24 days in dogs, 10 days in cats. It takes approximately 80–120 days to reach steady-state kinetics in dogs, 6 wk in cats.
5. The initial maintenance dose for potassium bromide is 20–35 mg/kg, orally once daily, or divided twice daily. If sodium bromide is used, the dose should be decreased by 15% (i.e., 17–30 mg/kg) to account for the higher bromide content of the sodium salt. The dose is subsequently adjusted based on clinical effects and therapeutic monitoring.
6. A loading dose is used if faster control of seizures is necessary.
 - a. Twenty-four-hour loading dose
 - (1) A total dose of 400–600 mg/kg of potassium bromide is administered orally over 24 hours.
 - (2) This is divided into doses of 100 mg/kg (the lower end of the range) q 6 hr for a total of four doses.
 - (3) If the patient appears obtunded prior to a dose, skip it and resume when the patient is alert again.
 - (4) After loading, begin the regular dose the next day.
 - (5) This schedule is used in patients that need adequate seizure protection immediately.
 - (6) The patient should be hospitalized for this loading procedure.
 - b. Five-day loading dose
 - (1) 450 mg/kg of potassium bromide is administered over five days.
 - (2) The daily loading dose (90 mg/kg) is added to the maintenance daily dose (35 mg/kg) for a total oral daily dose for each of the five days of 125 mg/kg/day. This dose should be divided BID to avoid gastrointestinal irritation.
 - (3) On day six, the maintenance dose is started.
7. A serum bromide level is checked within one week after loading or three months after starting a maintenance dose. Timing of sample collection is unimportant, because of the long half-life. The therapeutic range is 1–3

mg/ml for patients taking bromide alone and 1–2 mg/ml for those taking bromide and phenobarbital.

8. Bromide competes with chloride for renal elimination. High chloride intake increases bromide elimination, which increases the dose requirement. Thus, the chloride content of the diet should not be drastically altered during treatment.
9. Renal insufficiency decreases bromide elimination, so in dogs with persistent isosthenuria or azotemia, the initial dose of bromide should be halved and serum bromide concentrations monitored closely.
10. When adding bromide in dogs taking phenobarbital, the phenobarbital dose can be gradually tapered if the seizures are well controlled once the serum concentration of bromide is at least 1.5 mg/ml.
11. Side effects of bromide are usually dose-dependent and include pelvic limb stiffness and ataxia, sedation, vomiting, polydipsia/polyuria, polyphagia, hyperactivity, and pruritic skin rash. Uncommonly, behavioral abnormalities (e.g., aggressiveness) have been attributed to bromide administration. Rarely, pancreatitis has been associated with bromide use, either alone or in combination with phenobarbital. Chloride levels are often artifactually elevated on serum chemistry panel results, because the assays cannot distinguish between chloride and bromide ions.

C. Diazepam^{1,24,26–28,42,43}

1. Benzodiazepines are believed to exert anticonvulsant activity via enhancing GABA effects in the brain. Benzodiazepines are metabolized primarily by the liver. The half-life of diazepam is very short in dogs (2–4 hr) and it cannot be used in this species as maintenance therapy. Diazepam is used in dogs and cats intravenously or rectally for emergency treatment of seizures.
2. In cats, diazepam can be used as a maintenance drug (0.5–2.0 mg/kg/day, PO, every 8 or 12 hr). Fatal hepatic necrosis has been associated with oral diazepam in cats. Liver enzymes are checked at one week and one month after starting therapy.

X. Second-Line Drugs

A. Clorazepate^{1,26,27,44,45}

1. Clorazepate is a benzodiazepine drug which is sometimes effective when added to phenobarbital and/or bromide in dogs. Clinical experience in cats is limited.
2. The initial dose is 0.5–1.0 mg/kg orally every 8 hr. Sustained-delivery tablets are available but offer no advantage over regular-release tablets in dogs.
3. Serum levels tend to decrease with time, so subsequent dose increases are usually necessary. Long-term use of clorazepate may lead to the development of tolerance to antiseizure effects.

4. Clorazepate often increases phenobarbital concentrations, which can lead to side effects, so phenobarbital levels should be closely monitored.
5. Clorazepate is quite expensive.

B. Primidone^{30,46}

1. The efficacy of primidone is similar to that of phenobarbital in dogs. However, clinical experience suggests that primidone carries a greater risk of liver disease compared to phenobarbital. Therefore there is no reason to use this drug in dogs.
2. Primidone may be toxic to cats.

C. Felbamate (Felbatol)^{1,26-28,47-51}

1. Although clinical experience is limited, felbamate may improve seizure control in dogs refractory to phenobarbital and bromide. There are several proposed mechanisms of action for felbamate's anticonvulsant activity. These include enhancing actions of GABA in the brain, blocking of neuronal N-methyl-D-aspartate (NMDA) receptors, and reducing neuronal sodium currents. Approximately 30% of the oral dose of felbamate undergoes hepatic metabolism, the remainder being excreted in the urine. The half-life of elimination for felbamate in dogs is 5–6 hr. There is no clinical information available concerning the use of felbamate in cats.
2. The initial dose is 15 mg/kg every 8 or 12 hr. This can be increased in 15 mg/kg increments every 2 wk until seizures are controlled. Doses as high as 70 mg/kg every 8 hr are required and tolerated well in some dogs. The toxic dose of felbamate in dogs is 300 mg/kg/day.
3. Side effects are uncommon and this drug is not sedating. Nervousness and hyperexcitability can occur at high doses. Felbamate may increase the risk of liver dysfunction, especially in dogs taking other potentially hepatotoxic drugs.
4. Felbamate is very expensive.

D. Gabapentin (Neurontin)^{1,26-28,50-53}

1. Gabapentin is sometimes beneficial in dogs with seizures refractory to other drugs. Suspected mechanisms of action for gabapentin include inhibition of voltage-gated neuronal sodium channels, and enhancing the release or actions of GABA in the brain. Although gabapentin is completely renally excreted in humans, about 30% of the orally administered dose undergoes hepatic metabolism in dogs. The half-life of elimination of gabapentin in dogs is 3–4 hr. There is no clinical information available regarding the use of gabapentin in cats.
2. A recommended starting dose is 100–300 mg/dog every 8 hr. The dose is titrated upward every 1 to 2 wk until seizures are controlled or a maximum dose of 1200 mg every 8 hr is reached. Another recommended dosing schedule is 25–60 mg/kg, divided every 6–8 hr.

3. Side effects appear to be uncommon and gabapentin is not sedating.
4. This drug is very expensive.

E. Zonisamide (Zonegran)⁵⁴⁻⁵⁶

1. Zonisamide is a new sulfonamide-based anticonvulsant drug recently approved for use in the United States. Potential anticonvulsant mechanisms of action include blockage of T-type calcium and voltage-gated sodium channels in the brain, modulation of CNS dopaminergic metabolism, scavenging free radicals, enhancement of CNS GABA release, and inhibition of carbonic anhydrase. Zonisamide has been shown to be an effective anticonvulsant agent for focal and generalized epilepsy in people, as well as for experimentally induced seizures in several animal models.
2. Limited pharmacokinetic data are available for zonisamide in dogs. The drug undergoes hepatic metabolism; the half-life of elimination was reported as 15 hr in one study. Zonisamide use is characterized by minimal side effects in people. Side effects include drowsiness, ataxia, and gastrointestinal upset. A toxicity trial in Beagles demonstrated minimal side effects at dosages up to 75 mg/kg/day for 1 yr.
3. Based upon existing literature and limited clinical experience with the drug, a dose schedule of 10 mg/kg, every 12 hr for dogs is likely to achieve serum zonisamide levels within the therapeutic range for people (10–40 mg/L). The efficacy of zonisamide in dogs with seizure disorders remains to be determined.
4. Zonisamide is very expensive.

F. Levetiracetam (Keppra)⁵⁷⁻⁶¹

1. Levetiracetam is a new, pyrrolidine-based anticonvulsant drug. The mode of action of this drug is unknown. Some suspected modes of levetiracetam's anticonvulsant actions include inhibition of voltage-gated calcium channels, and ameliorating allosteric inhibition of GABA and glycine channels. Levetiracetam has exhibited efficacy in both people with seizure disorders and experimental animal models.
2. The half-life of elimination for levetiracetam in dogs is approximately 4 hr, and the drug is nearly 100% bioavailable following oral dosing (data on file @ UCB Pharma Inc). Despite the short half-life, there is evidence that the anticonvulsant actions of levetiracetam may persist for some time after serum drug levels have dissipated. Close to 70% of the drug is eliminated unchanged in the urine, the remainder being hydrolyzed in the serum and other organs. There is no hepatic metabolism of levetiracetam. Levetiracetam is very safe in dogs; salivation, restlessness, vomiting, and ataxic gait were observed at doses exceeding 400 mg/kg/day. These side effects resolved within 24 hr of drug discontinuation (data on file @ UCB Pharma Inc.).
3. Based upon limited clinical experience with levetiracetam in dogs, a dosage schedule of 20 mg/kg body weight, every 8 hr is recommended. The efficacy of this drug in canine seizure disorders remains to be determined.

4. Levetiracetam is very expensive.

XI. Ineffective Anticonvulsant Drugs^{1,26,27}

There are several drugs used in human patients that are ineffective in dogs, usually because of short elimination half-lives. These include phenytoin (dilantin), carbamazepine, valproic acid, and ethosuximide.

XII. Refractory Epilepsy^{1,30,36}

Epilepsy is refractory when the patient's quality of life is compromised by frequent or severe seizures despite appropriate drug therapy. Approximately 25% of dogs with epilepsy are believed to be refractory cases. In patients with apparent refractory epilepsy, it is essential to search for errors in diagnosis or management that may be responsible for treatment failure. Diagnostic errors include failure to recognize nonepileptic paroxysmal disorders and underlying causes for the seizures. A thorough history, careful examination, and appropriate use of ancillary diagnostic tests, such as imaging and cerebrospinal fluid analysis, helps avoid diagnostic errors. The use of ineffective drugs, incorrect dosing, and poor compliance are common causes of treatment errors. Therapeutic monitoring is helpful in identifying low blood concentrations caused by insufficient dose or poor compliance. Referral to a neurologist should be considered if seizures are not controlled after 3 mo of diligent therapy or if the diagnosis is uncertain.

XIII. Status Epilepticus and Cluster Seizures⁶²⁻⁷²

A. Status epilepticus

Status epilepticus (SE) is (1) a continuous seizure lasting at least 5 minutes or (2) two or more discrete seizures without full recovery of consciousness between seizures. This severe form of seizure activity is relatively frequent among dogs with idiopathic epilepsy, but can occur with seizure disorders of any etiology. Status epilepticus appears to be more common in large-breed dogs, and there may be a predominance in Labrador retrievers with idiopathic epilepsy. Status is a life-threatening emergency. Continuous seizure activity of 30 min or longer may cause systemic dysfunction, including hypoxia, altered blood pressure, and hyperthermia, and can lead to temporary or permanent brain lesions. The most common type of status epilepticus is generalized tonic-clonic status. With a prolonged seizure, the clinical manifestations can eventually become subtle, with only altered mentation and small twitching movements of the face or limbs. This situation is called electromechanical disassociation and should still be treated.

B. Cluster seizures

Cluster seizures (serial seizures, acute repetitive seizures) are two or more seizures occurring over a brief period but with the patient regaining consciousness

between the seizures. For practical purposes, the occurrence of more than three seizures in a 24-hr period should be considered an emergency condition that may evolve into status epilepticus and should be treated.

C. In-hospital treatment

1. Stop the seizure

- a. Administer diazepam at 0.5–1.0 mg/kg IV. Repeat for a total of three doses as necessary to stop the seizure. The duration of antiseizure effects is 30 min or less, so a longer-lasting antiseizure drug should also be administered (see below).
- b. If three doses of diazepam do not stop the seizure, there are several options:
 - (1) Administer propofol at 1–2 mg/kg IV. Be prepared to place an endotracheal tube and assist ventilation. Antiseizure effects can be maintained with a constant infusion of propofol at 0.1–0.6 mg/kg/min, titrated to effect.
 - (2) Administer pentobarbital intravenously at 2–15 mg/kg, IV, over several minutes, to effect. This drug enters the brain slowly, compared to diazepam, so allow several minutes to assess effects. Endotracheal intubation will be necessary.
 - (3) Administer phenobarbital at 2–6 mg/kg IV, to effect. This may take even longer to effect anticonvulsant action (15–20 min). However, some prefer this drug because it has more anticonvulsant activity than pentobarbital at doses that do not induce anesthesia.
 - (4) Induce general anesthesia with isoflurane.

2. Provide supportive care and initiate diagnostic evaluation

- a. Administer oxygen, usually by face mask in conscious animals or by endotracheal tube in unconscious patients. Assist ventilation as necessary.
- b. Place an intravenous catheter and obtain a blood sample to check glucose, calcium, PCV, and total solids. Hydration is maintained as necessary with fluid therapy.
- c. Monitor temperature and treat hyperthermia if necessary.

3. Prevent further seizures

- a. Start phenobarbital. Approximately 20 min are required for phenobarbital to enter the brain and exert antiseizure effects. If the seizures have stopped, and the animal is conscious enough to swallow, initiate oral phenobarbital at 3–5 mg/kg q 9–12 hr. If the patient cannot swallow or has a weak gag reflex, administer IM until awake enough to swallow.
- b. Some status/cluster patients may not be conscious enough to swallow orally administered drugs. Also, some patients may already have an adequate phenobarbital level at the time of the status/cluster episode, and need to be started on another drug. In these situations, intrarectal bromide can be administered as a loading dose over a 24-hr period. The loading schedule for liquid potassium bromide (KBr) per rectum is 100

mg/kg, every 4 hr for six doses (total of 600 mg/kg body weight). The bromide is administered via a syringe and red rubber feeding tube. This dosing schedule will effectively achieve a serum bromide level in the lower end of the therapeutic range. Rectally administered bromide is nearly 100% bioavailable. Side effects of this protocol include mild sedation and transient diarrhea.

- c. Seizure activity may resume. This is common because of the short duration of antiseizure effects with diazepam. After again stopping the seizure activity, there are several options:
 - (1) Diazepam infusion at 0.5–2.0 mg/kg/hr in 5% dextrose or 0.9% saline.
 - (2) Propofol infusion at 6 mg/kg/hr.
 - (3) Pentobarbital infusion: 0.5–4.0 mg/kg/hr. This needs to be carefully monitored, as it can cause cardiopulmonary depression. Also, many patients will seem disoriented with paddling during recovery from pentobarbital. This can be difficult to differentiate from a seizure.
 - (4) Phenobarbital infusion at 2–4 mg/kg/hr. This can also cause cardiopulmonary depression.
 - (5) Infusions are titrated to effect to control seizures. Blood pressure, body temperature, tissue oxygenation, and hydration are kept within normal limits. The patient is turned at least every 4 hr. Palpate the bladder and express if needed, at least three times daily. The patient is kept warm, clean, and dry. Some patients require heavy sedation for 24–48 hr, yet will still recover.

D. At-home treatment

1. Despite appropriate maintenance therapy, some patients, especially large dogs, tend to suffer cluster seizures that require emergency treatment. The resulting financial and emotional drain on the client is a common cause of euthanasia. Rectal administration of diazepam by the client is effective in decreasing the need for emergency veterinary treatment in these patients.
2. Rectal administration results in higher and earlier peak serum concentrations compared with either oral or intramuscular routes. The client administers 1 mg/kg diazepam parenteral solution per rectum using a 1-in. teat cannula or rubber catheter attached to a syringe. A dose of 2 mg/kg is recommended for dogs on chronic phenobarbital therapy, which increases benzodiazepine clearance. Treatment is administered at the first sign of a seizure and can be repeated for a total of three times within a 24-hr period.
3. If seizures continue or the patient appears excessively depressed, the client is instructed to seek urgent veterinary care.
4. Some pharmacists can compound diazepam suppositories, and a gel formulation of diazepam (Diastat) for rectal administration has recently become available for rectal administration in human patients. However, the absorption of these products has not been studied in dogs.

NARCOLEPSY⁷³⁻⁷⁶

I. Introduction

Narcolepsy is a syndrome characterized by abnormalities in the sleep-wake cycle including excessive sleepiness and cataplexy. Excessive sleepiness is manifested as waxing and waning drowsiness and abrupt onsets of falling asleep (sleep attacks). Cataplexy is a brief episode of flaccid paralysis, usually brought on by excitement or emotion.

II. Pathophysiology

Narcolepsy is inherited in the Doberman Pinscher, Labrador retriever, and miniature Poodle, and occurs sporadically in other breeds of dogs. A defect in the hypocretin receptor 2 gene has recently been identified in dogs with narcolepsy. Acquired brain lesions, such as encephalitis, are rare causes.

The pathophysiology is related to alterations in sleep-wake regulation associated with abnormal function of monoaminergic neurotransmitters. The locus coeruleus (slow wave sleep) and median raphe (fast wave, REM sleep) of the pons control sleep patterns. Neurotransmitters important in maintaining normal sleep patterns include norepinephrine, serotonin, dopamine, and acetylcholine. Narcoleptic patients have abnormally low CNS levels of norepinephrine, serotonin, and dopamine. Additionally, abnormal pontine cholinergic sensitivity has been demonstrated in narcoleptics. Cataplexy is similar to the normal muscle paralysis that occurs during the rapid eye movement (REM) phase of sleep.

III. Clinical Signs

The onset of signs can occur as early as four weeks of age but in mild cases signs may not become apparent until several years of age. Cataplexy is usually the most prominent sign. There are several characteristics:

- A. Episodes are typically elicited by excitement, such as food, water, or play, but can occur spontaneously.
- B. There is abrupt onset and termination of attacks.
- C. The duration varies from a few seconds to 30 min or more.
- D. There is partial to complete paralysis that may involve all muscles or be restricted to certain limbs or the head and trunk.
- E. Consciousness is preserved at the onset, but prolonged episodes can lead to REM sleep.

- F. Touching the dog or making loud noises can often terminate an attack.
- G. Excessive sleepiness is recognized in many affected dogs and has several manifestations:
 1. Prolonged periods of otherwise normal sleep.
 2. Difficulty arousing the patient during sleep.
 3. Apparent drowsiness throughout the day.
 4. A sudden onset of REM sleep from an active state (sleep attack). The patient is unconscious with closed eyelids and often has mild twitching of the face and distal limbs.

IV. Diagnosis

Diagnosis is based on the history, clinical signs, and the exclusion of other paroxysmal disorders, such as epilepsy, syncope, and myasthenia gravis. Response to treatment also supports the diagnosis.

V. Treatment

- A. Cataplexy is usually treated with antidepressants. The tricyclic antidepressants (imipramine, protryptiline, amitriptyline) act via blocking cellular norepinephrine reuptake in the CNS. Imipramine also blocks serotonin reuptake. Fluoxetine is a selective serotonin reuptake inhibitor. Dose recommendations for these drugs are listed below:
 1. Imipramine (0.4–1.0 mg/kg orally every 8 or 12 hr)
 2. Protryptiline (5–10 mg orally every 24 hr)
 3. Amitriptyline (1–2 mg/kg orally every 12 hr)
 4. Fluoxetine (1 mg/kg orally every 24 hr)
- B. Excessive sleepiness is usually treated with stimulants. Methylphenidate and dextroamphetamine are sympathomimetics. Selegiline is a monoamine oxidase B (MAO-B) inhibitor that acts to increase CNS dopamine levels. Dose recommendations for these drugs are listed below:
 1. Methylphenidate (0.25 mg/kg orally every 8 or 12 hr) often improves sleepiness and cataplexy.
 2. Dextroamphetamine (5–10 mg orally every 8 or 12 hr) may help with sleepiness and cataplexy.
 3. Selegiline (1 mg/kg orally every 24 hr) is also effective for excessive sleepiness, but not for cataplexy.

VI. Prognosis

Although there is no cure, medication is often effective in minimizing signs. The dose is titrated to effect. Some dogs improve without treatment.

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Chapter 7

DISORDERS OF HEARING AND BALANCE: THE VESTIBULOCOCHLEAR NERVE (CN VIII) AND ASSOCIATED STRUCTURES

Sean G. Sanders
Rodney S. Bagley

I. Functional Neuroanatomy of the Vestibular System¹⁻³

The vestibular system is a component of the nervous system responsible for the maintenance of posture and balance of the head and body. This system functions in close coordination with the cerebellum, with portions of the cerebellum providing similar functions as the vestibular nuclei. The components of the vestibular system can be anatomically and functionally divided into those found peripherally (outside of the brain stem), and those found centrally (within the brain stem and cerebellum). Separation of diseases affecting these two main areas is important both for differential diagnosis and prognosis in animals with vestibular system abnormalities.

The vestibulocochlear nerve is the only cranial nerve that does not exit the skull. The sensory neurons of both the vestibular and the auditory portion of CN VIII are bipolar neurons with cell bodies located in either the spiral ganglion (auditory) or the vestibular ganglion (vestibular) deep within the bony labyrinth of the petrous temporal bone.

Three components make up the bony labyrinth within the petrous bone (Fig. 7.1). These include the three semicircular canals, a vestibule, and the cochlea (which originates from the vestibule). The latter is important for auditory functions. The components communicate with each other and are filled with a fluid resembling cerebrospinal fluid, known as perilymph. These organs are comprised of membranous structures filled with another type of fluid, known as endolymph. Collectively, the organs are called the membranous labyrinth.

The semicircular ducts are located in the semicircular canal and are involved with vestibular function. The utricle and saccule are also involved with vestibular function and are located within the large vestibule. The vestibular labyrinths detect either static or kinetic positional signals.

The three semicircular canals are oriented at right angles to each other in order to detect angular movements of the head. The receptor of the semicircular ducts is the crista ampullaris. Like the macula, the crista ampullaris is covered by hair cells that project their cilia into a gelatinous structure known as the cupula. As the endolymph in the semicircular canals moves in relation to outside forces, the cupula moves and deforms the hair cells, which then stimulate the dendritic endings of sensory neurons of the vestibular portion of CN VIII. The crista ampullaris is a “kinetic” labyrinth because it senses the position of the head in any plane and rotational angle.

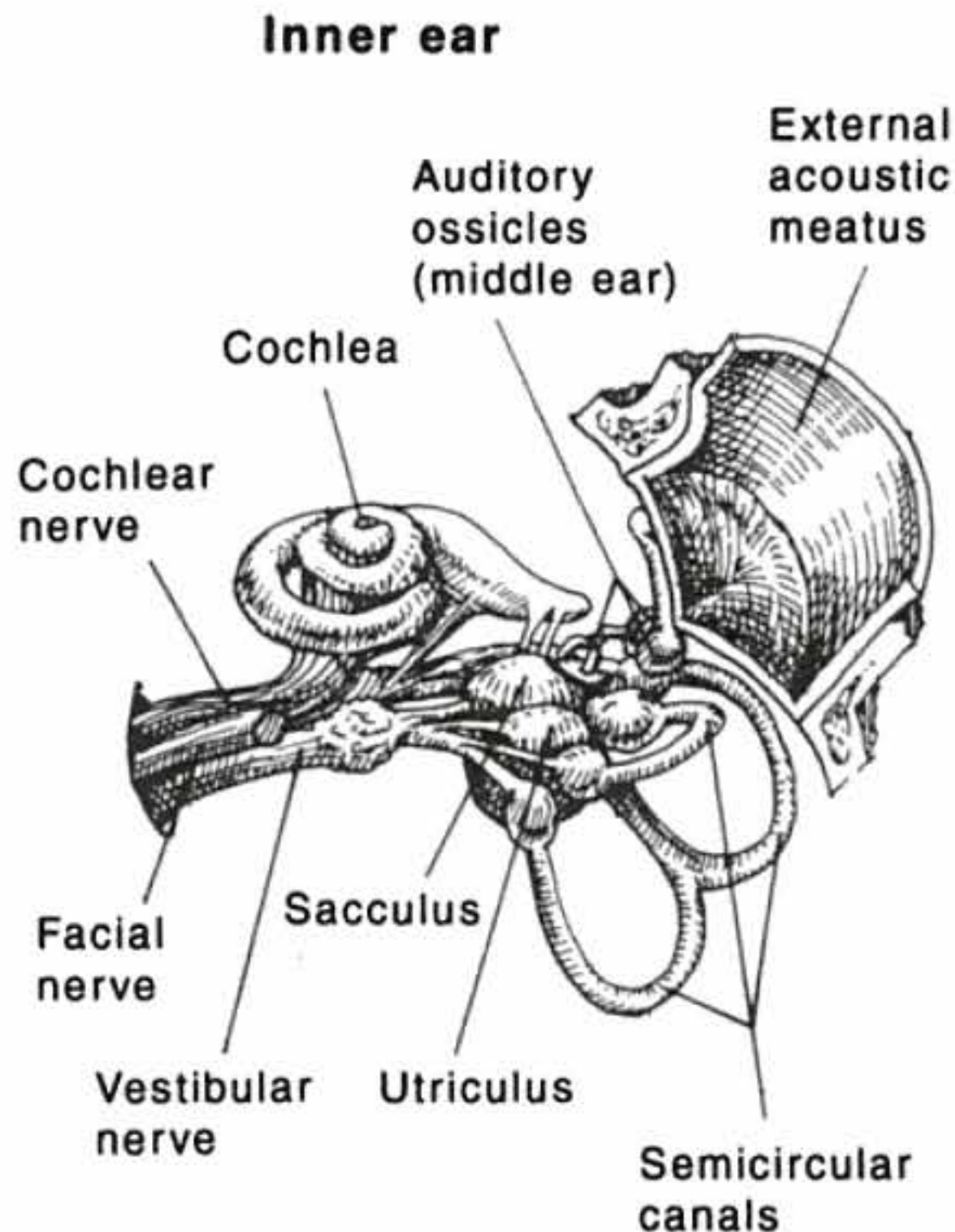


Fig. 7.1. Structures of the vestibular/auditory apparatus (Illustration by Carol Rudowsky).

The static labyrinths are the utricle (utriculus) and saccule (sacculus). The receptor of the utricle and saccule is known as the macula. The macula is covered by hair cells, which are the actual receptor cells. Along the luminal surface of the hair cells are cilia that project into a gelatinous substance known as the otolithic membrane. The otolithic membrane contains otoliths known as statoconia. As the otolithic membrane moves relative to gravitational forces, the hair cells are deformed. This generates an action potential that is propagated through the vestibular portion of the vestibulocochlear nerve (cranial nerve (CN) VIII). The utricle and saccule are responsible for localizing the static position of the head in space and in linear acceleration or deceleration.

Axons from neurons within the petrous temporal bone (i.e., spiral and vestibular ganglion neurons) enter the cranial vault through the internal acoustic meatus at the cerebellomedullary angle (rostral medulla oblongata). The combination of vestibular and auditory axons at this level comprises CN VII. These axons enter the brain stem at the level of the trapezoid body and caudal cerebellar peduncle.

Vestibular axons enter the brain stem and travel in several different pathways. The majority of the axons will synapse on the vestibular nuclei. A small number of axons will bypass the vestibular nuclei and ascend into the cerebellum via the caudal

cerebellar peduncle. Some of these axons will synapse on the fastigial nucleus and some of the axons will ascend into the cerebellar cortex into the ipsilateral flocculonodular lobe.

There are four vestibular nuclei on either side of the brain stem located in the ventrolateral wall of the fourth ventricle (Fig. 7.2). Axons from these nuclei project to the spinal cord and the medial longitudinal fasciculus (MLF). Fibers that descend the spinal cord are found primarily in the vestibulospinal tract (also referred to as lateral vestibulospinal tract) and mainly influence limb extensor tone. The vestibulospinal tract projects from the lateral vestibular nucleus to all levels of the spinal cord in the ipsilateral ventral funiculus (see Fig. 8.5). These axons will then synapse on interneurons in the ventral gray matter of the spinal cord to mediate facilitation of extensor muscles and inhibition of flexor muscles on the ipsilateral side.

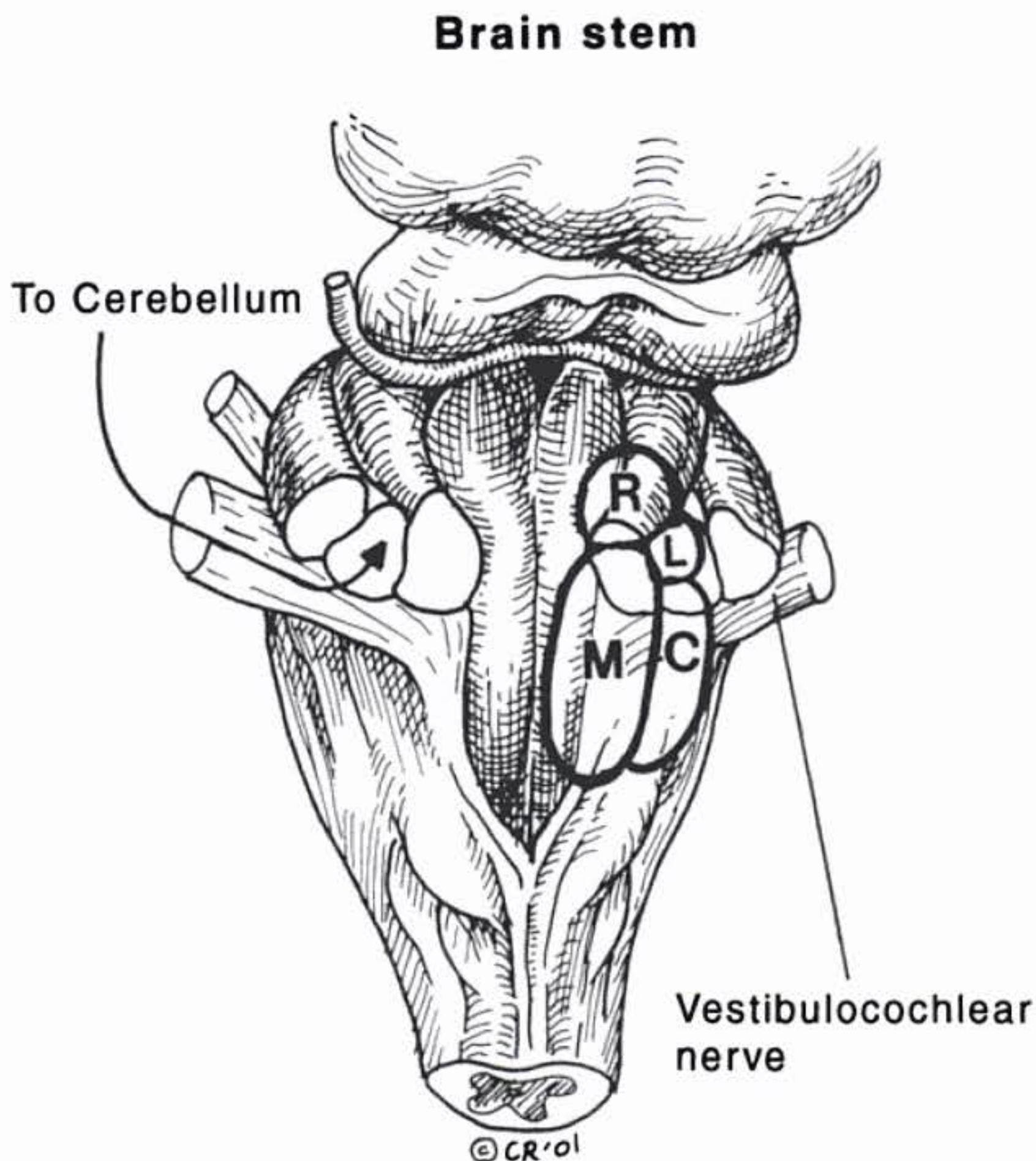


Fig. 7.2. Dorsal aspect of the brain stem. The cerebellum has been removed. M, medial vestibular nucleus; C, caudal vestibular nucleus; L, lateral vestibular nucleus; R, rostral vestibular nucleus (Illustration by Carol Rudowsky).

The medial longitudinal fasciculus (MLF) travels both rostrally to influence eye position and caudally into the spinal cord. The caudal or spinal limb of the MLF is sometimes referred to as the medial vestibulospinal tract. The group of axons that course rostrally will terminate within the nuclei of cranial nerves III, IV, and VI. This circuit influences the position of the eyes relative to the head in space and is responsible for the oculoccephalic reflex. The oculoccephalic reflex is the physiological nystagmus that is generated when the head is moved from side to side.

Within the spinal cord, the MLF, or medial vestibulospinal tract, is located in the ipsilateral ventral medial portion of the ventral funiculus. These fibers, in conjunction with the vestibulospinal (lateral vestibulospinal tract) pathways are responsible for maintaining the position of the body and limbs relative to the head. Finally, vestibular information is projected to other areas in the brain stem and cerebrum. The vomiting center, located within the reticular formation of the medulla, will receive afferent input from the vestibular portion of the vestibulocochlear nerve. These afferents likely play a role in motion sickness. A final pathway of the vestibular portion of CN VIII will ascend to the cerebrum along with portions of the cochlear nerve to provide a conscious awareness of the body's position in space.

II. Functional Neuroanatomy of the Auditory System^{2,4,5}

The sensory neurons of the auditory portion of CN VIII are bipolar neurons with their cell bodies located in the spiral ganglion within the bony labyrinth of the petrous temporal bone. The axons project to their respective receptor organs found in the bony labyrinth where their dendritic zones form synapses with mechanoreceptors (hair cells).

The auditory and vestibular receptors develop together embryologically and make up the inner ear. Sensory receptors for hearing are located in the cochlea in the organ of Corti. The cochlea is divided into three compartments. The two outside compartments contain perilymph. They are known as the scala vestibuli and the scala tympani. The middle compartment, known as the scala media or cochlear duct, contains endolymph secreted by the stria vascularis (the vascular endothelium lining one wall of the middle compartment of the cochlear duct). Between the cochlear duct and the scala vestibuli is the flexible vestibular membrane (Reissner's membrane). The cochlear duct contains the basilar membrane, along which the organ of Corti lies. The organ of Corti houses the receptors (hair cells) necessary for audition. The cochlear duct does not communicate with the outside compartments (scala vestibuli and scala tympani); however the outside compartments communicate with one another through an opening at the apex of the cochlea, known as the helicotrema. At the base of the scala vestibuli there is an opening to the middle ear. This opening is called the oval window or vestibular window (although it has nothing to do with vestibular function). The three ossicles (Latin for "little bones") are located in the middle ear. The first of these bones, the malleus is attached to the tympanic membrane.

As the tympanic membrane vibrates from sound waves in the outer ear, the vibrations are transferred to the malleus. The malleus is attached to the second ossicle, the incus. The incus is attached to the third ossicle, the stapes, which is attached

to the oval window. Because ultimately the goal will be to move the fluid in the cochlear duct, and since fluid resists movement much more than air, the ossicles act as an amplifier of the sound waves traveling through air to overcome the increased pressure necessary to move the fluid. The muscles of the middle ear, the *tensor tympani* (innervated by CN V) and the *stapedius* (innervated by CN VII) will reflexively contract in response to loud noises to dampen the activity of the ossicles and prevent damage to the inner ear. It is also thought that these muscles are active during vocalization in order to dampen the sound emanating from the pharynx. As the stapes pushes on the membrane of the oval window, perilymph in the scala vestibuli moves toward the helicotrema and deforms the vestibular membrane. Deformation of the vestibular membrane leads to a deformation of the basilar membrane secondary to compression of the endolymph within the cochlear duct. The distance that the compressive fluid wave travels along the basilar membrane will depend on the frequency of the sound. The basilar membrane is stiff and narrow at the base of the cochlear duct and becomes floppy and wide as it extends to the apex. A high-frequency sound will dissipate quickly at the stiff narrow end of the basilar membrane, while a low-frequency sound will travel far along toward the apex. Therefore, the longer the basilar membrane, the higher the frequency sound that will be perceived by the animal. Dogs have much longer basilar membranes than humans and are therefore able to "hear" higher frequency sounds (like a dog whistle). The area of the basilar membrane that is maximally deformed by the fluid wave will establish a place code for that frequency and produce maximal activation of the hair cells sitting atop the basilar membrane. The deformation of the hair cells will activate the dendrites of the auditory portion of the vestibulocochlear nerve.

Fibers from the cochlear portion of the vestibulocochlear nerve leave the spiral ganglion and enter the brain stem at the level of the junction of the medulla oblongata and pons, synapsing in the cochlear nucleus. From the cochlear nucleus, axons will either ascend the brain stem through the acoustic stria or cross midline in the trapezoid body (Fig. 7.3). In the caudal pons they may synapse in the dorsal or ventral trapezoid and some will continue on in the lateral lemniscus pathway (pons) to its termination in the caudal colliculus (midbrain). Efferents from the caudal colliculus will cross midline and descend to brain-stem lower motor neurons as tectobulbar projections to help mediate brain-stem reflexes. Some fibers will join the tectospinal tract, which originates in the rostral and caudal colliculus, and descends to the cervical spinal cord in the ventral funiculus. These fibers contain reflex information from both visual and auditory inputs in order to provide reflex movements of the head and neck in response to auditory and visual stimuli. The caudal colliculus is involved in reflex auditory functions. Auditory efferent axons will project from the caudal colliculus to the medial geniculate nucleus in the thalamus to mediate conscious auditory perception. The thalamocortical projections travel from the medial geniculate nucleus in the thalamus through the internal capsule and into the auditory cortex of the temporal lobe (cerebrum). The projections are predominantly contralateral; however, multiple areas of crossing of the pathways occur, so the representation of sound on each side of the cerebral cortex from the auditory system is rather diffuse.

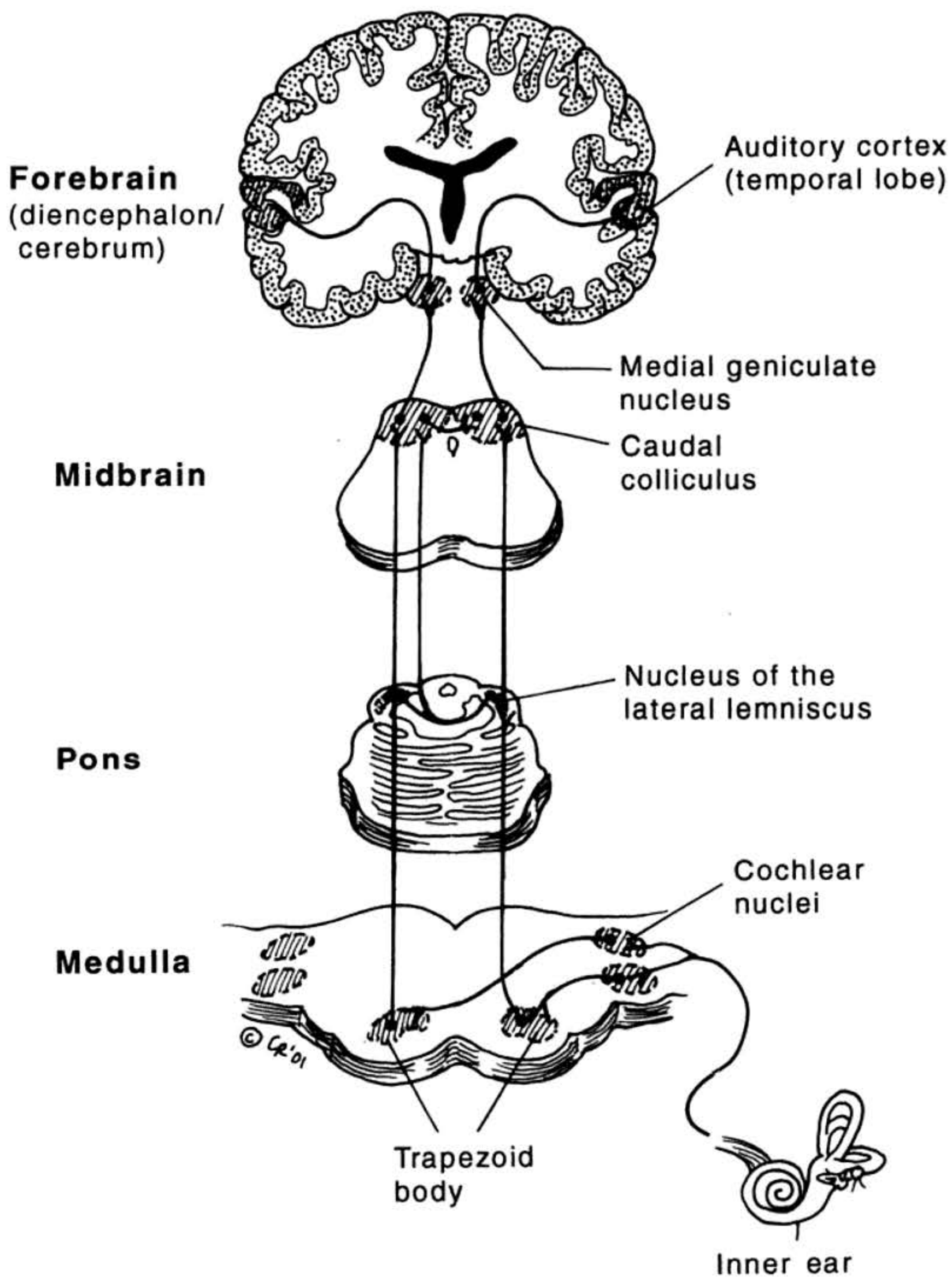


Fig. 7.3. Schematic representation of the auditory pathway (Illustration by Carol Rudowsky).

III. Clinical Evaluation of the Vestibular System^{2,4-8}

The vestibular system functions normally to maintain the animal's position in space. This coordinated activity of sensory input and reflex output is performed at a sub-conscious level. The maintenance of balance, posture, and tone contribute to normal equilibrium. The vestibular system is also intimately connected with the extraocular muscles responsible for reflex ocular movements and tracking objects in space. Signs of vestibular disease are usually manifested as unilateral or asymmetric ataxia. With pure vestibular disease, the strength of muscle contraction is normal.

Careful observation of the patient in a relaxed environment is very helpful when evaluating an animal for peripheral nerve disease. Allowing the patient to walk around the examination room and become accustomed to its surroundings may provide the investigator with important clues. Excessive barking or meowing may be appreciated in deaf dogs and cats. Of primary importance is the differentiation of peripheral from central vestibular disease. Behavioral changes (fear, aggression) or mental status changes (depression, dementia) are signs that indicate a central lesion. A thorough history along with a complete physical and neurologic examination are some of the most important diagnostic tools a clinician can have; however, without an adequate understanding of the anatomy and physiology of the vestibular system, even the most expertly performed neurologic examination is useless if not interpreted correctly. Additionally, false interpretations of a neurologic examination without additional diagnostic tests may lead to the unnecessary euthanasia of animals.

A. Clinical signs of vestibular dysfunction

The vestibular apparatus can be thought of as contributing equal, tonic input to each side of the head. When the vestibular nuclei are excited in the brain stem, there is ipsilateral facilitation of extensors and contralateral facilitation of flexors in the muscles of the limbs and trunk mediated via the vestibulospinal tracts. When the system is functioning correctly, the two opposing vestibular systems (left and right) balance each other out and the body's position in space is maintained at equilibrium. If a lesion prevents the activation of one side of the vestibular apparatus, then the ipsilateral vestibular nuclei will not be excited as much as the functioning, contralateral side. The imbalance in the system will cause relative facilitation of extensors on the normal side and lack of facilitation of extensors on the side of the lesion. Therefore, the body will be "pushed" by the normal extensors in the direction of the abnormality. This is manifested clinically as a head tilt, circling, leaning, falling, or rolling to the side of the lesion.

Because the vestibular system also contributes to the generation and maintenance of the oculovestibular reflexes, abnormalities of movements of the eyes can be very helpful clinically when trying to localize a lesion. When the head is rotated, the brain will try to keep the eyes focused on the visual field in order to keep the visual stimulus centered on the retina for optimal visual acuity. To perform this reflex activity, there is vestibular input to the brain-stem nuclei of cranial nerves III, IV, and VI. As the head is rotated, the extraocular muscles opposite the

direction of rotation will contract to “pull” the eyes back toward the center of the desired visual field. Once the muscles reach their limit, the eyes will quickly release and snap back in the direction of rotation and then again, slowly move back toward the center of the visual field. This reflex activity is known as the oculocephalic reflex and represents a form of *physiologic nystagmus*. Nystagmus is a rhythmic, involuntary, oscillation of the eyes. In the description above, the slow phase of the nystagmus was opposite the rotation. Nystagmus can have equal movements (no fast or slow phase), which is then referred to as *pendular nystagmus*, or it can have a fast phase and a slow phase, in which case it is referred to as *jerk nystagmus*. Pendular nystagmus is not a sign of vestibular disease. It is often observed in normal Siamese, Himalayan, and crosses of these breeds as a congenital defect in the visual pathways. When the vestibular apparatus is damaged on one side, there is an imbalance of neural activity in the vestibular nuclei, because the vestibular apparatus on the normal side continues to supply the vestibular nuclei with a constant signal. This imbalance is “interpreted” by the brain stem as rotation or movement of the body. A nystagmus will be generated, even though the body and head are stationary, with the slow phase directed toward the side of the lesion. By convention, the nystagmus is described by reference to the fast phase. A nystagmus can be characterized by the position the animal is in when the movement is generated and by the actual movement of the eyeballs themselves. For a postural description, the nystagmus may be spontaneous or positional. With a spontaneous nystagmus, the movement is present when the animal is in a normal postural position. With positional nystagmus, the involuntary eye movements are elicited when the animal is placed in an abnormal position, such as turned on its back or held upside down. The nystagmus may also be described based on the plane in which the eyeballs are moving. The movements can either be horizontal, vertical, or rotary. The nature of the movement (horizontal, vertical, or rotary) is dependent on which semicircular canal is affected. The vertical semicircular canals cancel each other out and, therefore, horizontal or rotary nystagmus is seen with peripheral vestibular disease. Because injury to the peripheral vestibular apparatus rarely involves one semicircular canal, usually, there are components of both rotary and horizontal nystagmus and the character may change between examinations.

Strabismus is an abnormal position of the eye. Strabismus is often present in dogs and cats with vestibular disease. This is usually seen as a deviation of the eye ventrally and laterally on the ipsilateral side. This strabismus may be positional (induced when the head is rotated dorsally) or spontaneous (always present). In some cases, the strabismus may be induced upon rotation of the head dorsally and then the eye slowly returns to the normal position of looking straight up at the examiner. This may be seen with careful observation of both eyes while looking for subtle differences in the position of the globe. This type of strabismus is not due to paralysis of any of the cranial nerves that innervate the extraocular muscles of the eye.

Motion sickness is rarely reported in dogs and cats, but probably occurs, especially in cases of acute vestibular dysfunction. Vomiting and salivation secondary to vestibular disease have been treated with various medications. Some are thought to have weak anticholinergic activity and therefore decrease the firing rate of the neu-

rons at the vestibular nuclei. The vomiting center is located within the reticular substance of the medulla and there are direct connections from the vestibular nuclei to the vomiting center. It is thought that by suppressing the activity of the vestibular nuclei, relief from motion sickness may result. Drugs that have commonly been used are the phenothiazine derivative chlorpromazine at a dose of 0.2–0.4 mg/kg SQ every 8 hr in dogs and cats, and the antihistamines diphenhydramine (Benadryl), dimenhydrinate (Dramamine), and meclizine (Antivert). A suggested dose for diphenhydramine is 2–4 mg/kg PO or IM every 8 hr in the dog or cat. Dimenhydrinate can be given at 4–8 mg/kg PO every 8 hr in the dog or cat. There are several suggested dosing regimens for oral meclizine: the authors recommend 25 mg every 24 hr for medium- to large-breed dogs and 12.5 mg every 24 hr for smaller dogs and cats. As always, contraindications and adverse side effects of each drug should be reviewed before administration.

B. Clinical localization of peripheral versus central vestibular disease.

There are numerous clinical signs that can help the practitioner in localizing a vestibular lesion. The primary goal is to decide if the problem is within the peripheral vestibular system or the central (brain) vestibular system. An accurate history, physical and neurologic examination are essential to success. The first priority is to determine if vestibular disease is a likely candidate for the animal's presenting signs. *A key component in the diagnosis of central vestibular disease is the presence of neurologic deficits that cannot be attributed to the peripheral nervous system alone.* Seizures, neck pain, tremors, and myasthenia gravis are often mistaken for vestibular disease. Animals with vestibular dysfunction will usually present with a primary complaint of head tilt, nystagmus, or ataxia (or combinations of all three). The key to differentiation between peripheral and central vestibular disease is to try and isolate the clinical signs to either involve only components of the peripheral vestibular system or include deficits that could only be explained by a central (brain) lesion. The deficits that may point the examiner in the direction of central vestibular disease include cranial nerve deficits (other than CN VII and CN VIII), vertical nystagmus, positional nystagmus, behavioral changes, seizures, and the presence of proprioceptive deficits.

A head tilt may be present with either peripheral or central vestibular disease. In the case of peripheral vestibular disease, the head tilt is always toward the side of the lesion. In the case of central vestibular disease, the head tilt may be toward or away from the side of the lesion (see discussion below of paradoxical vestibular disease).

Nystagmus that is either horizontal or rotary in nature could indicate either central or peripheral vestibular disease; however, the presence of a vertical nystagmus is highly suggestive of a central disease process. With peripheral vestibular disease, the fast phase of the nystagmus is away from the lesion. With central vestibular disease, the fast phase may be in either direction (toward or away from the lesion). The nystagmus is usually not positional with peripheral vestibular disease. Because animals are able to compensate rather well for peripheral vestibular disease, the nystagmus may only be present for a few days. With central lesions,

the nystagmus is often positional and it may change character (for example vertical to rotary) when the head position is altered. With bilateral peripheral vestibular disease, a nystagmus (or head tilt) will often not be present. These animals will appear as if they are getting ready to collapse. They will walk very tentatively with a low, crouched-down stance. Such patients may also display wide, side-to-side head excursions when ambulating.

The presence of strabismus is more of a "soft" finding when trying to differentiate peripheral from central vestibular disease. With peripheral lesions the strabismus tends to be ventral or ventrolateral on the same side as the lesion (ipsilateral). Strabismus is often positional, regardless of whether the causative lesion is peripheral or central. Extending the patient's neck (moving the head dorsally) often elicits a ventral or ventrolateral strabismus in patients with vestibular dysfunction. With a lesion in the central vestibular system, the strabismus may be deviating in various directions. Dysconjugate strabismus describes deviation of both eyes, but in different directions. This is an uncommon finding but is usually associated with central vestibular disease.

The facial nerve (CN VII) enters the internal acoustic meatus of the petrosal bone and courses through the facial canal to the point where it exits the skull (stylomastoid foramen) dorsal to the tympanic bulla. Because of its intimate contact with the peripheral vestibular system, disease processes such as otitis may affect facial nerve function. This may be manifested as complete or partial facial nerve paralysis or spasm. The sympathetic innervation to the eye also passes in close contact with the structures of the middle and inner ear. Therefore, the sympathetic system may be affected by peripheral vestibular disease and clinical signs of ipsilateral Horner's syndrome (ptosis, enophthalmos, miosis, and protrusion of the third eyelid) may be present. Deficits in facial nerve function or sympathetic innervation to the eye suggest a peripheral lesion, especially in the face of otitis or trauma to the same side.

The presence of cranial nerve deficits other than the facial or vestibulocochlear nerve is suggestive of a central problem. Alterations in mental status or level of consciousness may support a diagnosis of central vestibular disease based on the notion that vestibular projections to the reticular substance in the brain stem may be affected along with the neighboring ascending reticular activating system. The single strongest sign of central vestibular disease is the presence of conscious proprioceptive deficits. It is common to mistake ataxia for proprioceptive deficits (see Chapter 8). Ataxia may be present with both central and peripheral vestibular disease. Because the proprioceptive pathways do not come into contact with the peripheral vestibular system, alterations of conscious proprioception suggest a central lesion. Portions of the cerebellum add to the maintenance of posture and therefore, cerebellar signs along with vestibular signs suggest either brain-stem and/or cerebellar dysfunction. Clinical signs attributed to the forebrain (e.g., seizures, vision loss, behavioral changes) along with vestibular signs suggest a multifocal or diffuse disease process.

Paradoxical vestibular disease refers to lesions of the central vestibular system in which the head tilt is away from the lesion. The cerebellum normally sends

inhibitory efferent projections through the caudal cerebellar peduncle to the ipsilateral vestibular nuclei. If there is a lack of inhibition to the vestibular nuclei on the same side as the cerebellar lesion, the vestibular nuclei will be disinhibited, and through a similar mechanism as discussed previously, there will be greater facilitation of the extensors on the ipsilateral side and facilitation of the contralateral flexors. Therefore, the body will lean away from the side of the lesion and the head tilt will be in the opposite direction. In these cases, the fast phase of any resulting nystagmus will be toward the lesion. In many cases there will also be asymmetric conscious proprioceptive deficits. The lesion can be localized to the same side as the worst conscious proprioceptive deficits. Paradoxical vestibular disease can be seen with lesions of the flocculonodular lobes of the cerebellum, the caudal cerebellar peduncles, and the rostral and medial vestibular nuclei in the medulla. Occasionally, abnormalities in the dorsal nerve roots of C1–C3 will produce a paradoxical head tilt, and if present, conscious proprioceptive deficits will localize the lesion to the most severely affected side.

IV. Clinical Evaluation of the Auditory System

The ear canals of dogs and cats open within the second week of life; however, the complete maturation of the auditory system does not occur until 6 to 8 wk of age. Some estimates have put the maturation date at 4 to 8 wk. When assessing hearing in dogs and cats it is better to err on the conservative side and wait for complete maturation of the auditory apparatus. The entire auditory pathway, including the cerebral portions, is probably not completely matured until 12 wk of age. The clinical assessment of a suspected deaf animal can be difficult. Bearing this in mind, it is important to remember that all animals may react to vibratory clues (slamming a book on a table or shutting a door), or visual cues (clapping hands). Therefore, one should endeavor to stay out of the animal's visual field when trying to elicit an auditory perceived response. Complete hearing loss can be a challenge to assess clinically and partial or unilateral hearing loss is even more difficult to ascertain. Central deafness, or deafness due to an abnormality in the brain stem without concomitant signs of diffuse neurological disease, is rare. Because there are multiple points along the auditory pathways from the cochlear nuclei to the thalamus that cross, the auditory pathways are well represented bilaterally within the brain stem. It would therefore take a severe injury or disease process in order to completely disrupt auditory function. A process of that degree would certainly manifest itself with other signs of severe brain-stem disease. Therefore, complete bilateral deafness is usually caused by an abnormality with the auditory receptor (the organ of Corti) and more specifically with the hair cells themselves. The history and signalment of an animal suspected of having auditory dysfunction is very important. Especially pertinent are the breed of the dog and the age of onset when the owner first suspected a problem. This may help differentiate congenital deafness from acquired deafness, which may affect breeding programs. Other signs of neurologic disease, especially vestibular disease, are important to document, as well as any history of trauma to the head or ears, use of potentially ototoxic drugs or compounds, and any previous or current clinical signs of irritation (such as

head shaking, odor or exudates from the external ear canal). There are two types of deafness in dogs and cats: conduction deafness and sensorineural deafness.

A. Conduction deafness

When the middle or external ear is responsible for hearing loss, such loss is due to a problem with the actual conduction or transmission of the sound waves from the external environment to the cochlea. Blockage of sound wave transmission may be due to occlusion of the external ear canal by ceruminous debris, tissue, or foreign bodies. These blockages may be congenital, as in the case of birth defects, or acquired. Conduction blockage in the middle ear may be due to rupture of the tympanic membrane, fluid or exudate, excessive tissue growth, foreign body, malformation or damage to the ossicles, and stiffening of the ossicles with age.

B. Sensorineural deafness

If the inner ear auditory structures or auditory pathways are compromised, sensorineural deafness may result. Abnormalities of the cochlea, cochlear portion of the vestibulocochlear nerve, auditory pathways in the brain, thalamus, and cerebrum all have the potential to lead to a blockage of the auditory signal transmission and subsequent deafness. In all practicality, almost all cases of pure sensorineural deafness are due to a functional problem with the hair cells of the organ of Corti. There are no degenerative, congenital, or acquired conditions that specifically target the auditory pathways and projections in the brain.

V. Diseases Affecting the Peripheral Vestibular System^{2-5,8,14-16,33,48,60,63-74}

A. Degenerative/anomalous

Congenital vestibular disease: Peripheral vestibular disease may be evident in young animals and attributed to a congenital malformation or degeneration of the inner ear structures. If the abnormality is bilateral, these animals may not have a head tilt or nystagmus, however, they will frequently have a symmetrical ataxia, a wide-based stance, and a side-to-side movement of the head in the horizontal plane. The vestibular disease may be present in association with deafness. The clinical signs will usually present when the animals begin to ambulate. They may consist of head tilt, nystagmus, strabismus, ataxia, circling, falling, rolling, and abnormal head movements. Clinical signs associated with the vestibular disease may resolve; however, a head tilt or head tilt that shifts from side to side may persist. Many of the reported animals with this congenital peripheral vestibular disease will compensate for the abnormalities in balance. It is thought that any compensation is centrally mediated, likely through visual mechanisms. If the animal is deaf, the hearing abnormality is permanent. The abnormality has been known to affect German Shepherds, English Cocker spaniels, Doberman Pinschers, as well as Siamese and Burmese cats. In a report of Doberman Pinscher puppies affected from multiple litters from the same dam, a lymphocytic labyrinthitis was discovered on histological examination. An in utero viral infection was

hypothesized to cause the degeneration. No other abnormalities have been documented in affected animals. There is no treatment for the condition.

B. Metabolic

Hypothyroid-associated neurological dysfunction is well recognized. Specific involvement of the peripheral vestibular system may be the primary presenting clinical complaint. It is usually seen in older animals as an acute onset, nonprogressive presentation. Nearly all animals will have a head tilt and positional strabismus. Many animals also have decreased menace responses and decreased palpebral reflexes. More obvious signs of facial nerve paralysis may also be present. Other clinical signs may be an abnormal gait and circling. Brain-stem auditory evoked response testing may be abnormal. There may be other clinical and clinicopathological signs of hypothyroidism (hypercholesterolemia, abnormal TSH response). Other potential causes of vestibular disease must be ruled out, paying special attention to possible structural disease. Because the clinical signs associated with this disease may suggest central vestibular disease, the clinician should be certain a poor prognosis is not given to the owners of the animal without first evaluating and ruling out the possibility of hypothyroidism. The diagnosis may be challenging in that many animals are mistaken for euthyroid sick syndrome. With adequate supplementation of levothyroxine, the majority of these animals will return to normal.

C. Neoplastic

Neoplastic processes affecting the peripheral nervous system may result in peripheral vestibular disease by compression or invasion of the vestibulocochlear nerve. Peripheral nerve tumors (i.e., schwannomas) may initially present as peripheral vestibular dysfunction; however, with time they can invade the brain stem. Tumors of the ear (e.g., ceruminous gland adenocarcinoma) may invade the middle and inner ear and cause vestibular disturbances. Other tumors such as chondrosarcoma, osteosarcoma, fibrosarcoma, and squamous cell carcinoma have the potential to invade adjacent tissue resulting in vestibular disease. Treatment is directed at the primary lesion. Supportive treatment for vestibular dysfunction may also be necessary.

D. Idiopathic

A condition of idiopathic vestibular disease is well recognized in dogs and cats. Cats of any age can be affected. Dogs tend to be older and therefore the disease is often referred to as *idiopathic geriatric vestibular disease*. These vestibular episodes are often confused with vascular accidents ("strokes") or seizures. The key to this diagnosis is the absence of any detectable structural, metabolic or inflammatory disease, as well as lack of evidence of central disease. The onset is acute or peracute and animals may present with signs of dysfunction ranging from a mild head tilt to severe imbalance and rolling. The clinical signs are usually unilateral with a horizontal or rotary nystagmus (fast phase away from the side of the head tilt) and an asymmetrical ataxia. The ataxia may be confused with proprioceptive

deficits. Animals with idiopathic vestibular disease maintain their strength and mental status. The vestibular signs can be so severe that the affected animals are often incapacitated making the initial neurologic exam difficult, especially in cats. Most animals will improve rapidly, although complete recovery may take 2–3 wk in a typical case. Improvement is often appreciated within the first 72 hr. In some animals, clinical signs may persist for up to 5 wk. Occasionally, a mild head tilt will persist after other clinical signs have resolved. The condition can be relapsing. It is thought that this syndrome may result from abnormalities with the endolymphatic fluid of the inner ear structures, a mild intoxication of the vestibular system, or immune-mediated disease. There is no specific treatment for the disease. The use of corticosteroids has not resulted in more rapid clinical improvement. Care should be directed at supportive treatment, which may include sedatives, and therapy directed at relieving motion sickness. There is debate as to whether or not central signs (such as proprioceptive deficits) may be present with this clinical syndrome. Occasionally, in geriatric dogs with this disorder, pelvic limb conscious proprioceptive deficits will be demonstrated on neurologic examination. In many of these cases, the placing deficits are suspected to be due to chronic, subclinical disk protrusions unrelated to the vestibular disorder. However, until there is substantial improvement in vestibular function, or CNS disease is ruled out, pelvic limb conscious proprioceptive deficits should be considered potential evidence of a central vestibular disorder.

E. Inflammatory/infectious

The most common cause of peripheral vestibular disease in dogs and cats is otitis media/interna. It has been associated with approximately 50% of the cases of peripheral vestibular disease in older animals. The incidence is much lower in cats. The etiology of this condition is multifactorial. Otitis media/interna may develop from extension of otitis externa across the tympanic membrane, from the nasopharynx via the Eustachian tube, or hematogenously. In most cases, otitis externa is thought to develop as a secondary complication of various disease processes; such disorders include hypersensitivities (e.g., atopy, contact allergy, food allergy), parasites (e.g., *Otodectes cynotis*, *Demodex canis*), foreign bodies, and tumors. The most common infectious agents are *Staphylococcus* species, *Streptococcus* species, *Pseudomonas* species, *Proteus* species, and *Malassezia pachydermatis*. A complete, deep otoscopic exam is imperative. Additionally, a myringotomy with associated culture and sensitivity will direct the clinician to a proper treatment regimen. Radiographs or advanced imaging (CT/MRI) may confirm involvement of middle and inner ear structures. Occasionally, cases of otitis media/interna may extend centrally. In these cases, advanced imaging techniques such as magnetic resonance imaging may help the clinician to prognosticate, depending on the character of the lesion, and evaluate potential success of treatment. If myringotomy samples are not successful in the diagnosis of an etiologic agent and the animal does not respond to broad-spectrum antimicrobials, a bulla osteotomy may be indicated both as a treatment modality and to arrive at a definitive diagnosis of the etiologic agent. Most cats with polyp-associated otitis

media/interna will require a bulla osteotomy for resolution of clinical signs. General treatment of otitis media/interna consists of removal of any offending foreign bodies, adequate control of parasites, and usually long-term antibiotics or antifungals specifically directed at the offending organism(s) for 3–6 wk or until resolution of clinical signs. Occasionally, animals may need to be treated with medications directed at improving signs associated with motion sickness (e.g., diphenhydramine, dimenhydrinate). Any predisposing anatomic conditions may have to be addressed if the condition is chronic or relapsing (surgical resection or ablation of the ear canal). The prognosis for recovery is good if the damage to the receptor organs is not severe. Many animals will be able to centrally compensate for any residual vestibular deficits.

F. Toxic

The same toxic substances that may result in hearing deficits will affect the labyrinthine receptors of the vestibular system (see below at section VII C on disorders of hearing). Animals will usually present with signs of unilateral vestibular disease, although bilateral involvement is possible. The most common compounds are antimicrobials that belong to the family of aminoglycosides, loop diuretics (e.g., furosemide, ethacrynic acid), and ear-cleansing compounds. If toxicity is recognized early, and the offending compound is discontinued, vestibular signs may resolve.

G. Traumatic

Although uncommon, trauma to the petrous temporal bone may cause unilateral vestibular signs. Disruption of the bony and membranous labyrinth will predominate; however, if the injury is severe, other adjacent structures may be affected. It is much more common to have associated brain-stem, cerebellar, or supratentorial signs with trauma to this region of the skull. Ipsilateral facial nerve or trigeminal nerve dysfunction may also result. If the injury is mild, confined to the petrous temporal bone, or the animal heals from associated areas of trauma (brain stem or cerebellum), the prognosis for recovery from peripheral vestibular disease is good, providing central compensating mechanisms are adequate.

VI. Diseases Affecting the Central Vestibular System^{2,5,7,8,13,18,20,22,33,41,49,60–66,68,69,75–97}

Any disease process involving the brain has the potential to manifest itself with vestibular dysfunction. Alterations of normal vestibular pathways as a direct result of ischemia, compression, or infiltration will be secondary to the primary offending lesion. There are no recognized diseases of the central nervous system that specifically target the vestibular pathways, however, some of the disease processes that affect the vestibular structures do so preferentially.

A. Neoplastic

Any neoplastic process, whether primary or secondary, may affect portions of the nervous system involved with vestibular functions. Ischemia, compression, and

infiltration may all result from neoplasia. The clinical signs associated with the tumor may have an acute onset or be slowly progressive. They may result from a tumor in the immediate vicinity of the brain stem, or supratentorial masses that compress the diencephalon and cause secondary compression of the brain stem (either directly from brain parenchyma or via herniation). Tumors of the fourth ventricle such as choroid plexus papillomas, ependymal tumors, and epidermoid cysts may cause compression of adjacent brain-stem structures. Medulloblastomas originating from the cerebellum may affect the brain stem or the vestibulocerebellum. Oligodendrogliomas and astrocytomas may involve parenchyma directly associated with vestibular pathways. The most common brain tumors of dogs that affect vestibular function and associated brain-stem areas are meningiomas and choroid plexus tumors. Meningiomas and lymphomas are common neoplastic lesions in cats. The prognosis depends on many factors including location, tumor type, size, and systemic status of the animal. Treatment options include glucocorticoids to alleviate any peritumoral edema, chemotherapy, surgery, radiation therapy, or a combination of all of these (see Chapter 4, section III D, for more details concerning brain tumors).

B. Inflammatory/infectious

The canine distemper virus (CDV) may cause a distemper encephalomyelitis. Older dogs that develop distemper encephalomyelitis may present with an altered gait and vestibular disease. These dogs usually have an adequate vaccination history and diagnosis of canine distemper encephalomyelitis can be difficult. Cerebrospinal fluid may be characterized by a moderate mononuclear pleocytosis that is positive for the antibody directed at the canine distemper virus. It is important to realize that a breakdown in the blood-brain barrier may result in a false positive due to leakage of systemic antibody into the CSF. More specific information regarding diagnostic testing for CDV infection can be found in Chapter 4. Young dogs affected with distemper encephalomyelitis may recover from their systemic disease. In these cases, resolution of vestibular signs may follow. Cats infected with the feline infectious peritonitis (FIP) virus will often develop vestibular signs. Cats diagnosed with FIP usually have the dry form of the disease. A diagnosis is based on history, potential exposure, clinical signs, and the demonstration of a high CSF antibody titer directed at the feline coronavirus (see Chapter 4). There is no treatment for the disease and the prognosis is poor.

Dogs infected with the rickettsial agents causing Rocky Mountain spotted fever (RMSF) or ehrlichiosis may, among other clinical signs, develop vestibular dysfunction. The diagnosis of rickettsial infection will be based on potential exposure to ticks, hematological and biochemical abnormalities, clinical signs consistent with rickettsial disease, a single high titer, and/or a rising titer. Most cases will present between April and October with the highest incidence in the month of June. Rocky Mountain spotted fever is typically an acute onset infectious disease. Characteristic abnormalities may include anorexia, lethargy, fever, cutaneous lesions, ocular lesions, leukocytosis, anemia, thrombocytopenia, and

other signs referable to a vasculitis. Vestibular signs may include a horizontal nystagmus and ataxia. Early recognition and treatment with doxycycline will often result in complete resolution of the disease and vestibular signs.

Meningoencephalomyelitis resulting from primary bacterial infections is an uncommon occurrence in dogs and cats. When suspected, a CSF tap followed by culture and sensitivity is indicated. A combination of antimicrobials should provide broad-spectrum antimicrobial activity against most organisms if a specific etiology cannot be determined. Animals with an inflammatory CSF sample may benefit from low doses of prednisone (0.5 mg/kg BID). The anti-inflammatory activity of the prednisone may alleviate some of the inflammation responsible for the clinical signs. The dose is low enough that it should not severely inhibit the immune response and may be discontinued early in the course of treatment (see Chapter 4). Other infectious organisms such as *Toxoplasma gondii* and *Neospora caninum* can infect the nervous system and result in clinical signs that may include vestibular disease. Other clinical signs such as myalgia (due to myositis), paresis, and multifocal systemic involvement may predominate. Chapter 4 contains more information on the diagnosis and treatment of toxoplasmosis and neosporosis. Fungal infections involving the nervous system may be isolated to neural tissue; however, most animals will show other systemic signs of fungal disease including cutaneous, ocular, respiratory, and gastrointestinal disease. The most common fungal organism to involve the nervous system of dogs and cats is *Cryptococcus neoformans*. Coccidioidomycosis may be suspected in dogs with recent respiratory signs. Animals will often recover from a mild respiratory tract infection. There should be a history of being in the southwest United States. Another fungal infection that usually affects multiple organs is blastomycosis. Multifocal disease along with any indication for potential fungal infection (travel history, unresponsiveness to antimicrobials, etc.) should give the clinician cause to investigate possible fungal infection with attempts at direct visualization of the organism from infected tissues, CSF analysis, and serology. The prognosis depends on the duration of the infection and severity of clinical signs. Fluconazole is the antifungal of choice for cases of cryptococcosis and coccidioidomycosis. Very few animals show improvement with antifungal treatment for nervous system infection of blastomycosis. Disseminated protothecosis has been reported to cause vestibular signs in a dog. *Prototheca wickerhammi* and *Prototheca zopfii* have been identified as pathogenic species of algae. Although an uncommon infection, other clinical signs of multi-organ involvement are usually apparent. The prognosis for animals infected with protothecosis is poor.

It is thought that granulomatous meningoencephalomyelitis (GME) is a primary immune-mediated (autoimmune) disease. This disease may represent an immune response to an as of yet unidentified organism. There are disseminated (multifocal), focal, and ocular forms of the disease. The distinction between immune-mediated disease and neoplasia has been debated. This disease typically affects middle-aged, small-breed dogs. Brain-stem signs including vestibular dysfunction are the primary signs associated with the disease; however, clinical signs

would be referable to that portion of the nervous system that is most severely affected. In the vast majority of cases, a definitive diagnosis of GME can only be made on postmortem examination of affected tissue. The histologic lesions consist of perivascular granulomas comprised primarily of dense accumulations of inflammatory cells. Accumulations of histiocytes, lymphocytes, and plasma cells in the nervous system result in compression and invasion of surrounding tissue. A presumptive diagnosis may be made based on CSF analysis, by ruling out infectious etiologies, and demonstration of diffuse contrast-enhancing lesions on CT or MR examination. Lesions may not be evident on CT/MR images in GME cases. On CSF examination, there is usually a mononuclear pleocytosis and moderately elevated protein. Most animals will initially show a response to systemic corticosteroids; however, the remission of disease is usually short-lived. Radiation therapy may provide an effective treatment option. The prognosis for complete recovery is typically poor. The disseminated and ocular forms have the shortest clinical courses. Focal forms of the disease are often associated with longer survival times. More information regarding GME can be found in Chapter 4.

C. Toxins

Metronidazole has been associated with vestibular disease. The onset is acute and usually occurs when animals receive high doses for a long duration. There is much debate as to the toxic dose of metronidazole in the dog. Both dogs and cats are susceptible to metronidazole toxicity and the toxicity is well recognized in humans. Clinical signs of metronidazole toxicity usually show up 7–12 days after continuous high doses (greater than 60 mg/kg/day). The onset of clinical signs is likely dependent on the dose the animal is receiving. They may consist of generalized ataxia, nystagmus, anorexia, and vomiting. In severe cases, altered mental status, seizures, and opisthotonus may be present. Cats are typically affected by altered mental status and supratentorial dysfunction (seizures, blindness, and ataxia). Clinical signs will usually resolve within 1–2 wk after discontinuation of the drug. Some changes to the CNS may result in permanent neurologic deficits. Although a very effective antimicrobial, metronidazole is not innocuous. It is recommended that the dosage schedule be individualized for every animal, dependent upon the intended target of the drug. For most applications of metronidazole, a total daily dose of 30 mg/kg body weight (e.g., 10 mg/kg body weight, every 8 hr) is sufficient.

D. Miscellaneous

There are no degenerative processes that are known to specifically affect the central vestibular system. Vestibular dysfunction may result secondary to ischemic changes or direct trauma to the vestibular pathways. Hydrocephalic animals may have vestibular deficits which are part of the constellation of clinical signs that are commonly present (see Chapter 4). Metabolic disturbances such as hepatic encephalopathy, altered electrolyte balance, or renal disease may also cause sec-

ondary vestibular signs; however, these abnormalities would not likely cause isolated alterations in vestibular function. Rather, they would result in multifocal signs, of which vestibular signs may be part. Thiamine deficiency is a nutritional disorder that can affect the vestibular system. The deficiency may result from a diet that is deficient in thiamine, an all-cooked diet, or a diet that contains large amounts of thiaminase (fish viscera). Thiamine is necessary for the completion of the citric acid cycle and therefore is particularly important in tissues that rely on glucose for energy (brain). Thiamine deficiency primarily results in bilaterally symmetrical areas of necrosis, spongiosis, and hemorrhage in the brain stem. In cats the vestibular nuclei are often affected, resulting in vestibular signs. Cerebellar signs consisting of ataxia, tremors, and absent menace responses may also be seen. Because the heart is also very dependent upon glucose as a fuel source, it too may be affected. Bradycardia, tachycardia, and arrhythmias may be appreciated with thiamine deficiency. If diagnosed early many animals will respond to parenteral administration of thiamine hydrochloride (vitamin B₁). Many animals will have complete resolution of clinical signs if treated early.

VII. Diseases Affecting the Auditory System^{2-5,10-12,14,15,24-27,29-62,98-100}

Due to the close anatomical relationship between the auditory and vestibular receptors, abnormalities of hearing may be observed in conjunction with clinical signs of peripheral vestibular disease. As previously mentioned, a presumptive diagnosis of deafness is easier to make if bilateral disease is present.

A. Degenerative/anomalous

1. Congenital aplasia/hypoplasia of auditory receptors

Loss of hearing receptors either in utero or shortly after birth is a very common cause of deafness in dogs and cats. This is a pure sensorineural deafness due to degeneration of the hair cells in the organ of Corti. It is thought that an abnormality of the stria vascularis leads to a secondary degeneration of the hair cells. Once lost, hair cells are gone forever. Dogs and cats can be either unilaterally or bilaterally affected with partial or complete hearing loss, respectively. This form of deafness often affects white-colored dogs and cats, and merle or piebald-colored dogs. Nonwhite breeds of dogs can also be affected such as the Doberman Pinscher. High-incidence dog breeds include Dalmatian, English Cocker spaniel, English setter, Australian shepherd, Australian Cattle dog, and Bull terrier. Deafness may also be associated with blue eye coloration. White cats that have two blue eyes have a 50% chance of being born either unilaterally or bilaterally deaf. The incidence of deafness in Dalmatians is reported to be nearly 30%. Congenital deafness has been reported in many breeds (see Table 7.1), although not all have been shown to be hereditary. Because the degeneration of the organ of Corti may not take place until three weeks after birth, it is important to delay testing of young

Table 7.1: Dog and Cat Breeds Reported to Have Congenital Deafness

Canine	
Akita	Miniature Poodle
American–Canadian Shepherd	Mixed Breed Dog
American Eskimo	Norwegian Dunkerhound
American Staffordshire Terrier	Nova Scotia Duck Tolling Retriever
Australian Blue Heeler	Old English Sheepdog
Australian Cattle Dog	Papillon
Australian Shepherd	Pit Bull Terrier
Beagle	Pointer
Bichon Frise	Puli
Border Collie	Rhodesian Ridgeback
Borzoi	Rottweiler
Boston Terrier	Saint Bernard
Boxer	Schnauzer
Bull Terrier	Scottish Terrier
Cardigan Welsh Corgi	Sealyham Terrier
Catahoula Leopard Dog	Shetland Sheepdog
Cavalier King Charles Spaniel	Shropshire Terrier
Chihuahua	Siberian Husky
Chow Chow	Soft Coated Wheaten Terrier
Cocker Spaniel	Springer Spaniel
Collie	Sussex Spaniel
Dalmatian	Tibetan Spaniel
Dappled Dachshund	Tibetan Terrier
Doberman Pinscher	Toy Poodle
Dogo Argentino	Walker American Foxhound
English Bulldog	West Highland White Terrier
English Cocker Spaniel	Whippet
English Setter	Yorkshire Terrier
Fox Hound	Feline (associated with white coats)
Fox Terrier	European White
French Bulldog	Foreign White
German Shepherd	White Cornish Rex
Great Dane	White Devon Rex
Great Pyreneese	White Manx
Ibizan Hound	White Persian
Italian Greyhound	White Scottish Fold
Jack Russell Terrier	White Turkish Angora
Kuvasz	White American Shorthair
Labrador Retriever	White British Shorthair
Maltese	White Exotic Shorthair
Miniature Pinscher	White Oriental Shorthair

animals until their auditory apparatus has matured (6–8 wk). There is a syndrome of congenital deafness and vestibular dysfunction that has been reported in Beagles. Congenital deafness may also be the result of exposure to ototoxic drugs in utero.

2. Age-related hearing loss

Older animals may be affected by slowly progressive hearing loss. This senile degeneration may affect the ossicles of the middle ear, resulting in conduction deafness, or the auditory receptor (organ of Corti), resulting in sensorineural deafness. This may be mistakenly interpreted as cognitive dysfunction syndrome (see Chapter 4). A brain-stem auditory evoked response (BAER) test will confirm the dysfunction, usually seen as an attenuation of all waveforms and increased latency from stimulus to appearance of wave I (hearing impairment), or absence of waveforms (complete deafness). Senile ossicle or receptor dysfunction usually has a slow progression and there is no treatment for the progression of the condition; however, hearing aids may be used in animals. The success of a hearing aid is dependent on the tolerance of the animal to having a foreign body constantly in its ear. Placing inexpensive foam earplugs in the animal's ear to see if it will accept the more expensive hearing aid is a good way to test potential tolerance to a hearing aid.

3. Structural anomalies of the brain

Hydrocephalus and other anomalous structural conditions that affect the brain may affect auditory function. These dogs may have difficulty localizing sound due to poor development of higher auditory centers. Structural brain anomalies are discussed in Chapter 4.

B. Inflammatory/infectious

Peripheral vestibular disease is often a result of otitis in dogs and cats. It is one of the most common conditions diagnosed as causing secondary vestibular disease. Otitis may only affect the external ear (otitis externa), the middle ear (otitis media), the inner ear (otitis interna), or combinations of these three locations. A thorough otoscopic examination is essential for diagnosis. A normal otoscopic exam does not rule out otitis as a potential cause of either hearing loss or vestibular disease. Otitis externa or media may cause a conduction block, resulting in a hearing deficit of the affected ear. Otitis interna may be severe enough to cause sensorineural hearing deficits. Some of the more common isolates from the ear are *Streptococcus* spp., *Pseudomonas* spp., and *Staphylococcus* spp. Treatment should be based on results obtained from culture and sensitivity testing. Long-term (e.g., 4–6 wk) treatment with systemic antimicrobials is often necessary. In addition to systemic antibiotics, otitis externa may be treated with topical antimicrobial preparations and routine ear canal lavage. Occasionally, surgery is necessary in refractory cases. Surgical procedures include ear canal resection, total ear canal ablation, and bulla osteotomy. Nasopharyngeal polyps are often associated with otitis media in cats. These proliferative tissue growths originate from the lining of the tympanic cavity and often grow toward the path of least resistance, the

pharyngotympanic (Eustachian) tube. They can often be seen within the nasopharynx. Cats will usually have clinical signs referable to a nasopharyngeal mass (e.g., sneezing, gagging) in addition to hearing loss, vestibular dysfunction, and possibly ipsilateral Horner's syndrome. They may be plucked from the nasopharynx or, preferably, removed surgically via a ventral bulla osteotomy. Nasopharyngeal polyps are much less likely to recur if removed via ventral bulla osteotomy.

C. Toxic

There are numerous known and suspected ototoxic agents, which may cause vestibular signs and deafness. Often the vestibular dysfunction is reversible upon withdrawal of the compound; however, deafness is usually permanent. The most commonly incriminated compounds are the aminoglycoside antimicrobials and ear-cleaning solutions. Many of the suspected ototoxicities are anecdotal. Ototoxic substances may gain exposure to the inner ear via a ruptured tympanic membrane when applied topically, or hematogenously. Once in the middle ear, the substance enters the inner ear through the oval or round window. Toxin-mediated destruction may involve the cochlea, the semicircular canals, or the vestibule and typically affects the hair cells either directly or indirectly via alteration of the stria vascularis. Many commonly used ear-cleaning solutions may be ototoxic if applied in an ear with a ruptured tympanic membrane. Possible substitutions for ceruminolytic agents are dilute acetic acid (white vinegar) and saline at a 1:3 ratio or saline alone. If hearing loss or vestibular disease is suspected due to a potential ototoxic agent, the use of the compound should be discontinued immediately. Prognosis for recovery will depend on the age, species, breed, general health status, time of use, and application of use.

D. Traumatic

Unilateral deafness secondary to trauma is possible. Trauma rarely results in complete deafness. The petrous temporal bone may fracture and injure the vestibulocochlear nerve. The higher auditory centers may also be affected by cranial trauma; in these cases there would likely be signs of diffuse and severe neurologic impairment (see Chapter 5).

E. Miscellaneous

A rare condition called otoacoustic emission (OAE) has been reported in several dogs and one cat. This disorder is similar to tinnitus of people. In addition to their normal function of converting sound waves to mechanical vibrations, the outer hair cells of the cochlea are apparently able to generate sound by vibrating. The etiology of OAE is unknown. Typically, a continuous high-frequency ringing tone can be heard emanating from the affected ear. Behavioral responses to sound are normal in affected patients, as are BAER tests. There is no known effective treatment for OAE, but the disorder does not appear to pose any adverse effects on health.

VIII. Diagnostic Tests^{2,4,5,8-29}

A. Peripheral disease

When a suspected peripheral nerve disease is presented, a thorough otoscopic exam should be performed to completely evaluate the outer ear. An otoscopic exam may also give clues to the examiner regarding the integrity of the middle ear. A bulging, discolored tympanic membrane may be indicative of otitis media. If so equipped, an otoscope with a side port may be used to subjectively test the compliance of the tympanic membrane with a gentle "puff" of air. The authors use a short piece of rubber tubing attached to the port on the head of the otoscope. While visualizing the tympanic membrane, a gentle puff of air is blown into the tubing and the tympanic membrane is observed to see how much deformation occurs. If the middle ear is fluid filled or occluded by tissue, the compliance of the tympanic membrane will be decreased. A thorough otoscopic exam almost always requires general anesthesia. This examination can be performed in conjunction with other diagnostic tests that require general anesthesia (e.g., radiographs, CT, MRI, CSF tap).

Indirect evaluation of the auditory system is possible utilizing electrodiagnostics. The brain-stem auditory evoked response (BAER, see Chapter 3) test is one method of evaluating the auditory pathways. This test is usually performed in awake dogs and cats; however, it can also be performed with mild sedation or anesthesia, if necessary. The potentials that are measured result from a far field recording of an evoked response. To perform this test, clicks or tones are generated in the ear of the animal and the response of the brain stem and auditory pathways is recorded via needle electrodes placed on the scalp and near the ear. The test generates an early latency waveform within 1–10 ms, indicating various activities within the brain. With peripheral disease, there would be attenuated or absent waveforms. This does not differentiate between conduction block and sensorineural block. However, a bone resonator can be used to stimulate the cochlea directly by placing it on the mastoid process of the temporal bone (junction of nuchal crest and caudal aspect of the zygomatic arch). A conduction block may be differentiated from sensorineural block because the mechanical vibrations generated by the resonator will themselves activate the receptor organ directly, effectively bypassing the external and middle ear cavities. The BAER is able to evaluate both ears. Most animals with bilateral deafness can be diagnosed with confidence based on a thorough physical and neurologic exam. An animal with unilateral deafness will often appear normal clinically, and therefore can only reliably be diagnosed by performing a BAER.

Some less-frequently performed diagnostic tests include impedance audiometry–tympanometry and testing of the acoustic reflex. Tympanometry can be used to evaluate the size of the internal ear, the integrity and compliance of the tympanic membrane, and the function of the middle ear components (ossicles and muscles). In this test, a tube is inserted into the external auditory canal that delivers both an auditory stimulus and pressure changes. The ear canal is sealed and

the changes in pressure reflected back from the tympanic membrane inside the sealed cavity are measured. The curve of the tympanogram will tell the examiner information about the compliance of the tympanic membrane. An abnormally high compliance (flabby tympanic membrane) would result from damage to the ossicles. An abnormally low compliance (stiff tympanic membrane) may result from otosclerosis. The acoustic reflex is a protective mechanism to prevent damage to middle and inner ear structures. The reflex is mediated through the afferent arm of the cochlear nerve. The efferent portion is generated via both the facial nerve, which innervates the stapedius muscle, and the trigeminal nerve, which innervates the tensor tympani muscle. When a loud noise is received by the inner ear, the reflex contraction of the middle ear muscles prevents excessive displacement of the ossicles, which could damage the ear. Of course there is a delay in the reflex; very loud, sudden noises may cause significant damage.

Imaging techniques for evaluating the peripheral vestibular system and auditory components are rather limited. Radiographs of the skull may provide the clinician with the "footprints" of disease, such as sclerosis of the external acoustic meatus and bulla. These may prompt the examiner to take a closer look at the problem; however, lack of evidence of bony changes does not rule out the possibility of disease. Computed tomography greatly enhances the evaluation of the bony components of the peripheral nervous system by providing transverse images through the area of interest. Magnetic resonance (MR) imaging can be performed and provides the ability to look at changes in the bulla, allowing one to distinguish between fluid and soft tissue abnormalities (including the presence of polyps). On MR imaging, the air-filled bulla would appear hypointense (black). The reader should refer to Chapter 3 for more information concerning MR imaging.

If a case of otitis media/interna is suspected, a myringotomy may be performed. This diagnostic test requires general anesthesia. A needle is used to puncture the tympanic membrane, and fluid, if present, is aspirated and evaluated through cytology, culture, and sensitivity. The tympanic membrane will heal from this procedure, if performed correctly.

B. Central disease

The BAER test can be helpful in differentiating central from peripheral vestibular disease. If the sound waves can get to the organ of Corti, and the animal is not deaf, then the evoked response should be visible as a series of waves that represent brain-stem activity. The exact locations of the generation of the waves in the brain are not completely known. It is well agreed upon that the generator of the first wave is the vestibulocochlear nerve. The other waves typically visualized (waves II–V) represent various nuclei and pathways for auditory function in the brain (see Chapter 3). The latencies (time necessary for the generation of the wave following a stimulus), amplitude, and morphology (right vs. left) of the waves are evaluated. The first wave will often be present followed by abnormal waves and increased interwave intervals (latencies) in cases of central vestibular disease. The

BAER has also been used to evaluate brain death, often in conjunction with electroencephalography (EEG).

Radiographs may be of benefit when evaluating an animal for suspected skull trauma. Because of anatomic variations and difficulty with correct positioning and interpretation, skull radiographs do not provide a high level of diagnostic information regarding central vestibular disease. Computed tomography (CT) will allow the clinician to evaluate the skull and brain in the transverse (axial) plane. Contrast may be added to demonstrate any break in the blood-brain barrier. Computed tomography may be a better diagnostic tool for evaluating bone; however, an MR exam will allow for adequate evaluation of bone and superior evaluation of soft tissue, and will potentially save a second anesthesia if no abnormalities are seen on CT examination. It is the best test for the evaluation of structural brain disease. Magnetic resonance imaging will give a multiplanar evaluation of brain structures, is noninvasive, and is rapidly performed in the hands of a skilled technician. The drawbacks to MR examination are both a paucity of facilities in which the test can be performed and the limited access to personnel adequate in their evaluation. Most major cities and universities will have access to animal-dedicated MR facilities within the next few years. A diagnosis of inflammatory brain disease can only be made with cerebrospinal fluid (CSF) analysis. The authors typically perform this test following MR evaluation of the brain. It has been hypothesized that in the face of increased intracranial pressure, a cisternal tap may alter the homeostasis of pressure relationships in the brain, which may lead to secondary brain-stem herniation (transtentorial or foraminal). In cases of large structural abnormalities (mass effect), a lumbar tap may decrease the chances of herniation (although it is not eliminated). This potential advantage of performing a lumbar versus cisternal CSF tap remains to be proved. Although many cisternal taps have been performed in the face of large, compressive brain masses, with no complications, caution should be used. Evaluation of cerebrospinal fluid is discussed in Chapter 3.

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Chapter 8

CEREBELLAR DISEASES AND TREMOR SYNDROMES

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CEREBELLAR DISORDERS

I. Introduction¹⁻¹⁰

The cerebellum is unique both structurally and functionally within the central nervous system. Although only occupying approximately 10% of brain parenchyma in dogs and cats, it is responsible for the efficient and accurate processing of motor function. A basic understanding of the cerebellum's role in the nervous system is helpful when considering how pathology within the cerebellum affects clinical functions. The cerebellum is responsible for modification of, rather than the initiation of, movement. The cerebellum functions to coordinate segmental movements so they are fluid in nature and to aid in ensuring movements are achieved in an efficient manner. The cerebellum helps to regulate posture, proprioception (the position of the body in space), and muscle tone. The cerebellum is also thought to influence conscious thought processes, such as judging the timing of events and solving spatial and perceptual reasoning problems.

II. Divisions of the Cerebellum^{1-3,8,9,11-13}

The cerebellum can be conceptually divided in numerous ways, according to developmental, anatomical, and functional features. Depending upon the clinical situation, and clinician preference, an understanding of the cerebellum can be framed in the context of these different categorization schemes.

Phylogenetically, the cerebellum can be divided into three parts. The *archicerebellum* is the oldest part and is composed of the flocculonodular lobe. The *paleocerebellum* is next in line, and consists of the most rostral portion of the cerebellum, rostral to the primary fissure. Finally, the *neocerebellum* is the newest and largest portion of the cerebellum, and is composed of the hemispheres and paravermal portion caudal to the primary fissure.

Anatomically, the structure of the cerebellum contains the two lateral hemispheres, a median portion (the vermis), and a small ventral portion, the flocculonodular lobe. The superficial surface folds of the cerebellum are known as folia (Fig. 8.1). On cut section, the cerebellum has many branching, infolded sections known as arbor vitae (meaning "tree of life"). Embedded within the deep white matter are the three-paired "roof" nuclei. From medial to lateral these are known as the fastigial, interposital, and dentate (Fig. 8.2). The dentate nucleus is also referred to as the lateral nucleus in some texts. These nuclei are synaptic centers for both afferent and efferent information. The cerebellum makes up the dorsal half of the metencephalon

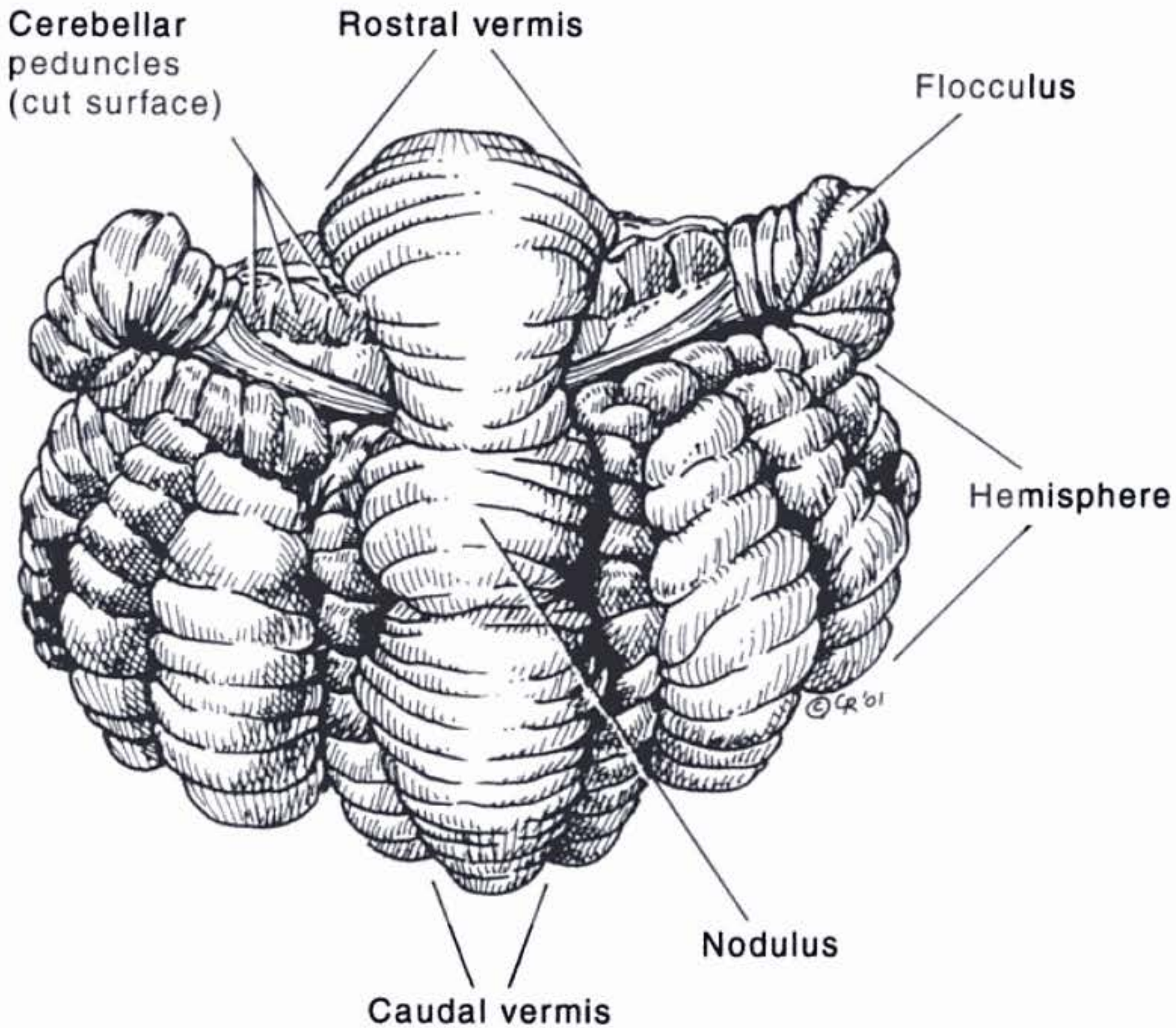


Fig. 8.1. Gross anatomy of the cerebellum, ventral aspect (Illustration by Carol Rudowsky).

with the pons comprising the ventral half. The cerebellum is attached to the brain stem by the three paired cerebellar peduncles, which act as conduits for both afferent and efferent information related to cerebellar function.

Finally, and probably most important, the cerebellum can be functionally divided into the cerebrocerebellum, spinocerebellum, and vestibulocerebellum. Each functional division can be related to its associated anatomical structures (Fig. 8.3). The cerebrocerebellum consists of the cerebellar hemispheres, is associated with the dentate nucleus, and is primarily responsible for limb movements. This portion of the cerebellum is necessary for the implementation of voluntary, planned, multi-joint movements. Additionally, the cerebrocerebellum is involved in the cognitive process of the intention to move. Studies have shown that neurons of the dentate nucleus fire before the onset of movement and before the neurons in the cerebral motor cortex that are responsible for that particular movement. In general, the cerebrocerebellum is required for the control of movement direction, timing, and force. It accomplishes this function through influencing the cerebral cortex motor output.

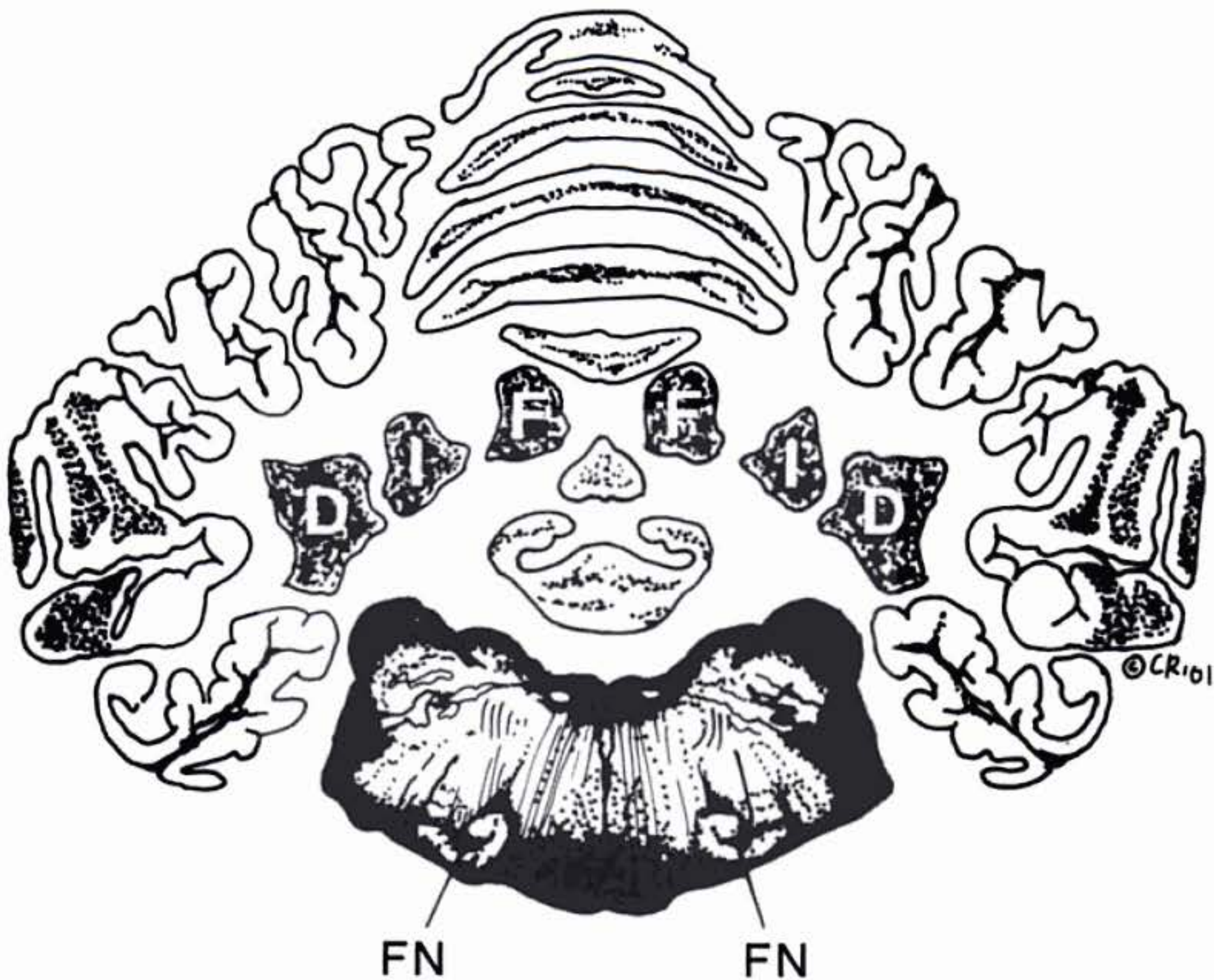


Fig. 8.2. Cut section of cerebellum. Deep cerebellar nuclei are from medial to lateral fastigial (F), interposital (I), and dentate (D). Facial nucleus at level of cerebellomedullary junction (FN) (Illustration by Carol Rudowsky).

The spinocerebellum is composed of the vermis and the intermediate zone (medial portions of the hemispheres). This division of the cerebellum is associated with the fastigial and interposital nuclei. It is primarily responsible for regulating muscle tone and unconscious motor movements necessary for posture and gait.

The vestibulocerebellum is made up of the flocculonodular lobe (the nodulus and two flocculi). The vestibulocerebellum is associated with the fastigial nucleus. This portion of the cerebellum primarily projects to the vestibular nuclei of the brain stem. It is principally responsible for the maintenance of equilibrium and coordinating movements of the head and eyes.

III. Microscopic Anatomy of the Cerebellum^{1-3,11,12,14}

The inner portion of the cerebellum is the medullary substance. It contains the deep cerebellar nuclei. The outer portion is the cerebellar cortex. The cerebellar cortex is made up of three distinct layers. From outer to inner these are the molecular cell

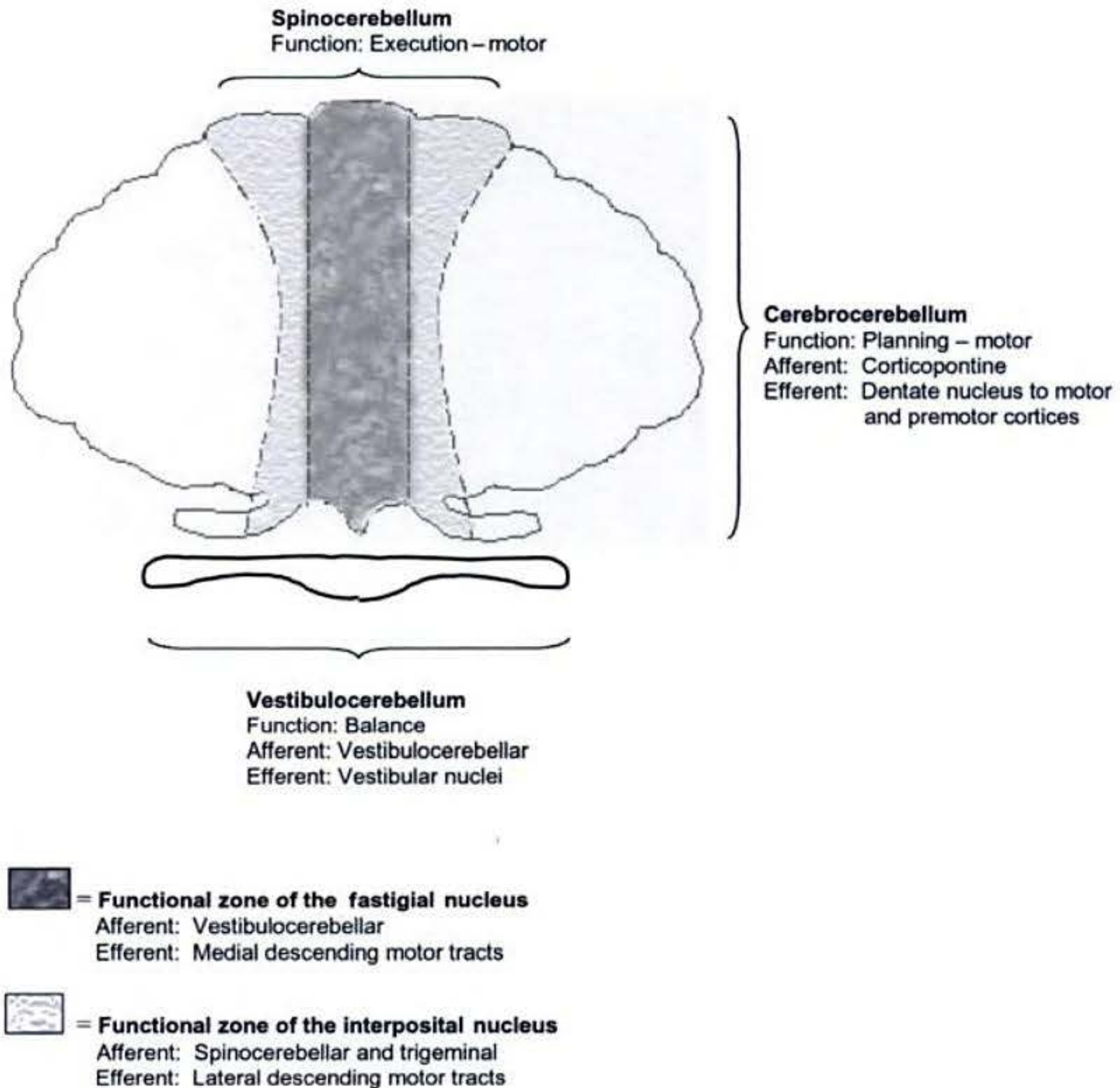


Fig. 8.3. Functional divisions of the cerebellum.

layer, the Purkinje cell layer, and the granule cell layer (Fig. 8.4). The sophisticated arrangement of the cells that make up these layers allows the cerebellum to distinguish between errors in movement and the intended movement. The complex interactions of the distinct synapses allow the cerebellum to recognize both temporal and spatial events.

The molecular layer is a comparatively cell-free area. It contains two distinct cell types and the axons of neurons from the granule layer that send their projections to the molecular layer (parallel fibers). The cells are known as basket cells and stellate cells. Both cell types are inhibitory. The axons of basket cells descend to the Purkinje cell layer and make terminal arborizations with Purkinje cell bodies. The stellate cells make synaptic contacts with Purkinje cell dendrites that extend into the molecular layer.

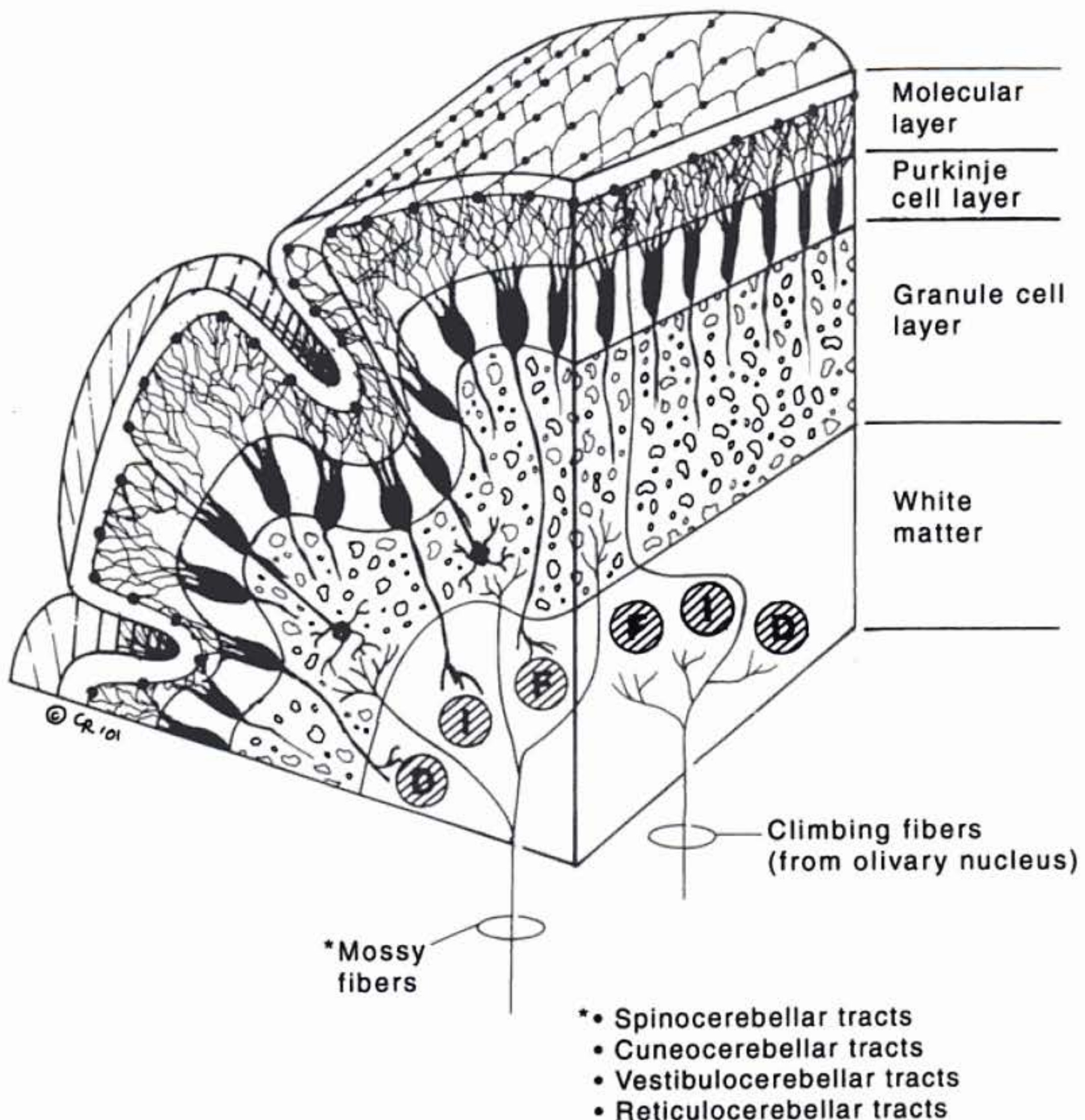


Fig. 8.4. Cellular arrangement of the cerebellar cortex. Deep cerebellar nuclei are from medial to lateral, fastigial (F), interposital (I) and dentate (D) (Illustration by Carol Rudowsky).

The Purkinje cell layer contains the highly ordered and uniformly arranged large cell bodies of the Purkinje cells. This layer, located between the molecular layer and the granule cell layer, contains the cells responsible for the output of the cerebellum. Purkinje cells are large, highly metabolically active, and therefore very susceptible to ischemic or toxic damage. These inhibitory neurons utilize gamma-aminobutyric acid (GABA) as their neurotransmitter. The myelinated axons of Purkinje cells leave the cerebellar cortex to synapse on the deep cerebellar nuclei. Along the way, these axons will send collateral projections off in the granule cell layer to synapse on neurons located there. Additionally, the Purkinje cells will send fanlike dendritic processes into the molecular layer. These projections run perpendicular to the parallel fibers in the

molecular layer. The parallel fibers run through the dendritic processes of the Purkinje cells much like electrical wires running through a bushy tree, making cross synapses with the Purkinje dendrites as they travel throughout the molecular layer.

The deepest layer of the cerebellar cortex is the granule cell layer. Two types of neurons are present there: the granule cells and the Golgi cells. This layer is filled with densely packed cells that look like lymphocytes when Nissl stained. The granule cells have unmyelinated axons that ascend to the molecular layer where they function as parallel fibers making cross synapses with the Purkinje dendrites (the electrical wires through the bushy trees). Golgi cells are located in the upper portion of the granule cell layer. They are inhibitory neurons, which utilize GABA as their neurotransmitter. Dendrites from the Golgi cells extend throughout all layers of the cerebellar cortex. Their axons form specialized synapses at the cerebellar glomeruli. The glomeruli are chiefly made up of axonal endings of mossy fibers (one of the two types of afferent projections into the cerebellum). Dendrites and axons from the Golgi cells, as well as dendrites from the granule cells, will synapse in the cerebellar glomeruli.

IV. Afferent Projections to the Cerebellum^{1-5,11,12,14}

The cerebellum receives sensory information from the entire nervous system yet projects its regulatory information to specific areas of the brain and spinal cord. The three different functional subdivisions of the cerebellum each receive primary information from specific portions of the nervous system (Fig. 8.3). The main contributions to each subdivision will be discussed; however, it is important to realize that afferent information to the cerebellum is distributed to all subdivisions with varying degrees. The *cerebrocerebellum* (hemispheres) receives input from the cerebral cortex via the pons (corticopontine fibers). Axons of the corticopontine fibers originate from the cerebral cortex, synapse on the deep pontine nuclei, cross midline as the transverse fibers of the pons, and ascend through the middle cerebellar peduncle. This information assists the cerebrocerebellum with motor planning.

The *vestibulocerebellum* (flocculonodular lobe) primarily receives afferent projections from the vestibular labyrinth indirectly via the vestibular nuclei in the medulla, and directly via connections from the vestibulocochlear nerve (cranial nerve (CN) VIII). It also receives information from the lateral geniculate nuclei and rostral colliculi via the pontine nuclei (corticopontine tracts). All information entering the cerebellum from the pontine nuclei ascends through the middle cerebellar peduncle. This information will help the cerebellum with balance (both while standing and ambulating) and eye movements.

The *spinocerebellum* (vermis and intermediate zone) receives afferent information regarding joint position and lower motor neuron status from the spinal cord (spino-olivary tracts, spinocerebellar tracts and cuneocerebellar tracts).

The neural pathways are named from their origination in the nervous system to their termination. For example, the spinocerebellar tracts originate in the *spinal* cord and terminate in the *cerebellum*; therefore they are termed *spinocerebellar*. In general, the spinocerebellar tracts convey information from the limbs and body to the ipsilat-

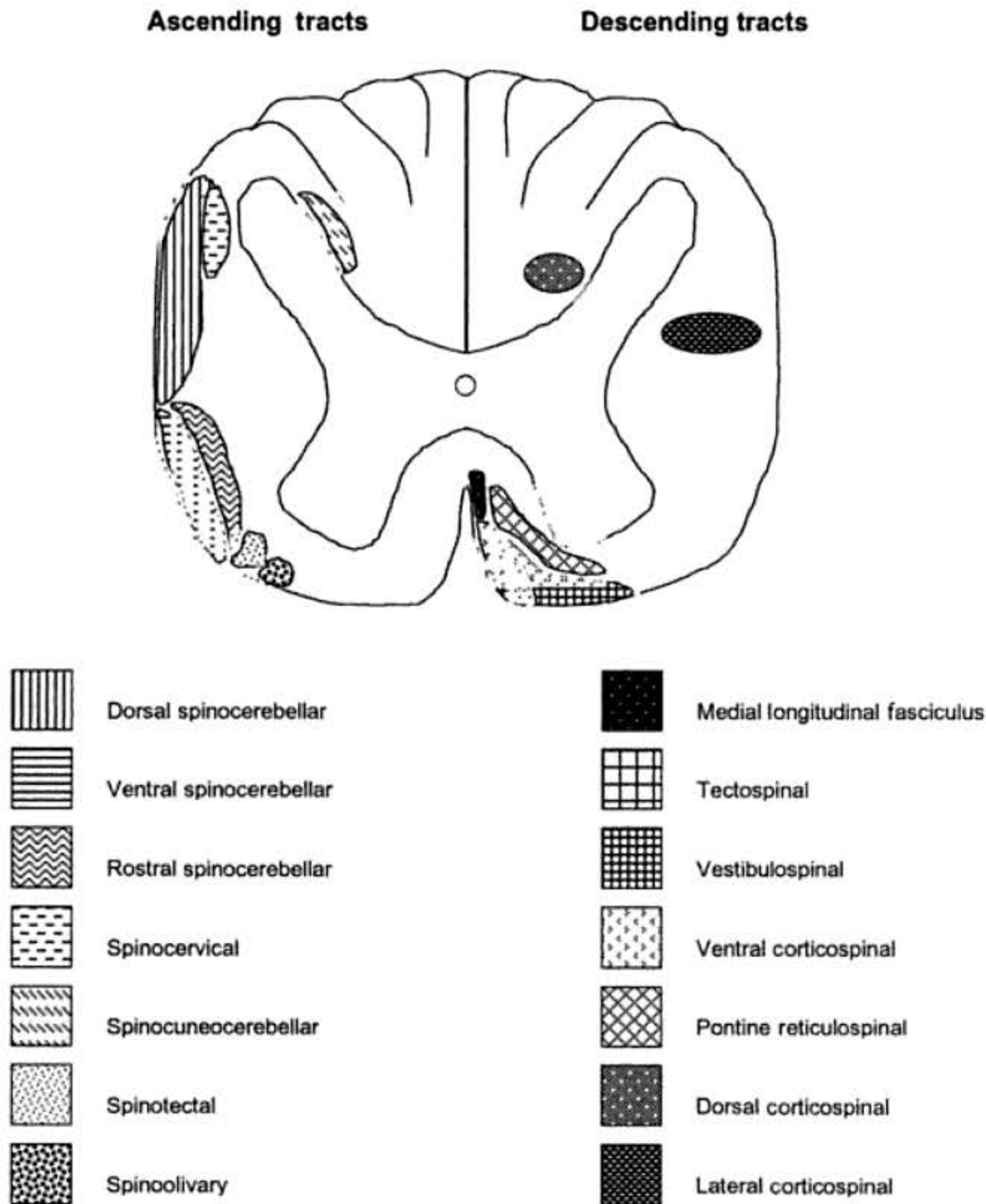


Fig. 8.5. Transverse section through the spinal cord showing the ascending and descending spinal tracts related to the cerebellum.

eral cerebellum. The dorsal spinocerebellar tract sends information from cutaneous, muscle, and joint receptors regarding proprioception from the pelvic limbs and caudal region of the body. This tract is located in the dorsal lateral funiculus (Fig. 8.5). The information is projected to the ipsilateral cerebellum and enters via the caudal cerebellar peduncle. The ventral spinocerebellar tract, which also conveys information from the pelvic limbs and caudal body region, is also located in the lateral funiculus. It sends information from muscle receptors and Golgi tendon organs, which ultimately reaches the ipsilateral cerebellum (after crossing midline twice) via the rostral cerebellar peduncle. The spinocuneocerebellar tract (cuneocerebellar tract), located in the dorsal lateral funiculus, primarily sends proprioceptive information from cutaneous, muscle, and joint receptors, from the ipsilateral thoracic limb and cranial part of the

body. It projects to the cerebellum via the caudal cerebellar peduncle. It is named by its synaptic connections with the *lateral cuneate* nucleus in the medulla (rostrolateral to the medial cuneate nucleus), where spinal projections synapse prior to entering the cerebellum. The rostral spinocerebellar tract (medial to the ventral spinocerebellar tract) also conveys information from the thoracic limbs and cranial aspect of the body. Axons of this tract enter the ipsilateral rostral and caudal cerebellar peduncles. The cervicospinocerebellar tract is a pathway conveying proprioceptive information from the neck region (first four cervical spinal cord segments) to the contralateral caudal cerebellar peduncle. The axons of this tract synapse in the rostral vermis. The cerebellum indirectly (via the pontine nuclei) receives visual and auditory information through the collicular nuclei via the middle cerebellar peduncle and vestibular input from the vestibular nuclei via the caudal cerebellar peduncle. This information is organized somatotopically and represents entire maps of the body projected in the region of the vermis and intermediate zone of the cerebellar hemispheres.

All of the projections to the cerebellum are either mossy fibers or climbing fibers (Fig. 8.4). These excitatory fibers alone control the activity and therefore the output of the Purkinje cells. For the most part, afferent axons enter the cerebellum through either the caudal or middle cerebellar peduncles. In general, information from the pons (metencephalon) enters the cerebellum through the middle cerebellar peduncle and information from the medulla (myelencephalon) enters through the caudal cerebellar peduncle. Exceptions include the ascending proprioceptive information from the pelvic limbs coursing in the ventral spinocerebellar tract, and a portion of the ascending information from the thoracic limbs conveyed by the rostral spinocerebellar tract. These axons enter the cerebellum through the rostral cerebellar peduncle.

Mossy fibers primarily originate from the spinal cord, reticular formation, vestibular nuclei, and pontine nuclei. They indirectly influence the firing of Purkinje neurons through their interactions with granule cells in the granule cell layer. The granule cells are excitatory interneurons. The interaction of mossy fibers and granule cells occurs at the cerebellar glomeruli where mossy fiber terminals come into contact with Golgi cell axons and granule cell dendrites. A single mossy fiber will typically activate a cluster of granule cells, the axons of which will ascend into the molecular layer. Along the way the granule cell axons will send off collaterals to Purkinje cells. Once in the molecule layer, these granule cell axons will become parallel fibers where they then again have the opportunity to interact at cross synapses with the Purkinje dendrites that extend into the molecular layer.

Three additional fiber types innervate all areas of the cerebellar cortex. All of these fibers enter the cerebellum as mossy fibers. One of the fiber types originates from the locus ceruleus and releases norepinephrine. These fibers interact directly with Purkinje cells. The second fiber type originates from the raphe nuclei and contains serotonin. These fibers do not synapse on Purkinje cells. Both of these fibers are thought to possibly play a role in emotional states and cerebellar function. A third fiber type originates from undefined brain-stem nuclei and releases acetylcholine.

Climbing fibers originate from a single source, the olivary nucleus (rostral myelencephalon). The olive receives descending input from the cerebral cortex and brain-stem upper motor neuron centers, as well as ascending input from the ventral

spinocerebellar tract. Information from the olivary nucleus projects to the cerebellum sending off collaterals to the cerebellar nuclei and continues into the Purkinje cell layer to form direct excitatory contact with Purkinje neurons. A Purkinje neuron receives input from a single climbing fiber and a single climbing fiber will interact with several Purkinje neurons. Of all the excitatory synapses in the central nervous system, the climbing fiber's interaction with the Purkinje neuron is one of the most powerful. An action potential from a climbing fiber will produce a prolonged depolarization of the target Purkinje cell. While mossy fibers rely on temporal and spatial summation to excite a Purkinje neuron, the climbing fiber can accomplish this with a single action potential.

V. Efferent Projections from the Cerebellum^{1-5,9,11,15}

As stated previously, the only output of the cerebellum is via Purkinje axons. The Purkinje neurons exert an inhibitory influence on the tonically active deep cerebellar nuclei. As with the afferent organization, the efferent projections from the cerebellum can be categorized based upon the three major subdivisions (Fig. 8.3). Purkinje neurons from the most lateral subdivision, the *cerebrocerebellum*, project to the most lateral cerebellar nuclei, the dentate nucleus. From the dentate nucleus, fibers descend through the *contralateral* rostral cerebellar peduncle to the ventral lateral nucleus of the thalamus. By crossing back to the contralateral rostral peduncle, the cerebrocerebellar projections will project to the ipsilateral cerebral cortex. As described earlier, the corticopontine fibers, which project to the cerebrocerebellum, cross in the pons to project to the contralateral cerebrocerebellum; the efferent projections cross back to maintain an ipsilateral circuit. The thalamic projections influence the motor and premotor areas of the cortex. Additionally, the dentate nucleus sends projections to the red nucleus in the mesencephalon. These projections form a complex feedback circuit back to the cerebellum through the olivary nucleus. They do not make up any portion of the rubrospinal tract (a descending spinal projection that originates from the red nucleus). The efferent projections of the cerebrocerebellum are responsible for the coordination and planning of limb movements. Some of the *vestibulocerebellum's* Purkinje neurons project directly to the vestibular nuclei in the medulla. These arise primarily from the flocculonodular lobe. Neurons of the fastigial nucleus also project to the vestibular nuclei. The vestibular nuclei give rise to the lateral and medial vestibulospinal tracts, which run in the ventral funiculi of the spinal cord white matter (Fig. 8.5). The main output is necessary for control of axial and proximal limb muscles in order to maintain balance. Vestibulocerebellar projections are also responsible for coordinated eye and head movements, as well as vestibular reflexes.

The *spinocerebellum's* output is projected through the fastigial and the interposital nuclei. The fastigial nucleus receives output from the vermis. Some of these fibers ascend to the cerebral cortex; however, most efferents descend to the vestibular nuclei and the reticular formation, both of which contribute fibers to the medial descending motor systems. The interposital nucleus receives output from the intermediate zone (medial hemispheres). Axons of the interposital nuclei continue on to influence lateral descending motor tracts. The areas of the cerebellum contributing to the medial

descending motor pathways are responsible for the regulation of axial and proximal musculature. Axons from the interposital nuclei descend through the rostral cerebellar peduncle to the contralateral red nucleus. They continue to the ventral lateral nucleus of the thalamus and eventually the cerebral motor cortex. These projections help to regulate the function of distal limb muscles by exerting their influence on both the corticospinal and the rubrospinal tracts, which are two of the lateral descending motor pathways. Efferents of the spinocerebellum coordinate the actions of axial and limb muscles to smooth out intended movements and dampen oscillations of ongoing movements.

VI. Functions of the Cerebellum^{1,2,4-6,8,16-32}

The cerebellum has traditionally been thought of as a modulator or regulator of movement initiated by the cerebrum. Experiments have shown that neurons in the dentate nucleus (cerebrocerebellum) actually begin firing before neurons in the cerebral motor cortex that are responsible for the intended movement. Neurons in the fastigial and interposital nuclei (spinocerebellum) fire after the movement has begun and their activity is directly related to the velocity and force of the movement. This suggests that the cerebrocerebellum is actually involved with the intention to move and therefore linked to cognitive function at some level, while the spinocerebellum monitors the consequences of the evolving movement. It is well accepted that the cerebellum plays a much greater role in an animal's cognitive awareness and output related to its environment.

The roles of the cerebrocerebellum and spinocerebellum in the initiation and execution of movement can be hypothetically mapped out (Fig. 8.6). The upper loop involves the cerebrocerebellum, which is important, along with the premotor cortex, for the programming of future movements. The lower loop involves the spinocerebellum, which, along with the cerebral motor cortex, regulates evolving movements.

The cerebellum is responsible for the optimization of motor performance. To that end, it plays an important role in "learning" the most efficient method for the initiation, execution and modification of conscious and unconscious movements. The firing of Purkinje neurons is modified indirectly through the action of mossy fibers on climbing fibers, so that in a sense, the climbing fibers are "teaching" the Purkinje neurons to generate a new response.

VII. Clinical Signs of Cerebellar Dysfunction^{1-5,9,33,34}

Clinical signs of cerebellar dysfunction can generally be referred to as abnormalities in the rate, range, direction, and force of motor movements. Lesions of the cerebellum typically result in ipsilateral deficits. This physiological phenomenon is due to the fact that output through the rostral cerebellar peduncle is crossed and primarily acts to modify movement generated through the corticospinal and rubrospinal tracts, which are also crossed. Pure cerebellar disease does not result in paresis (weakness). There are usually no conscious proprioceptive deficits; however, during a neurologic evaluation, it is important to consider that a specific lesion may involve multiple

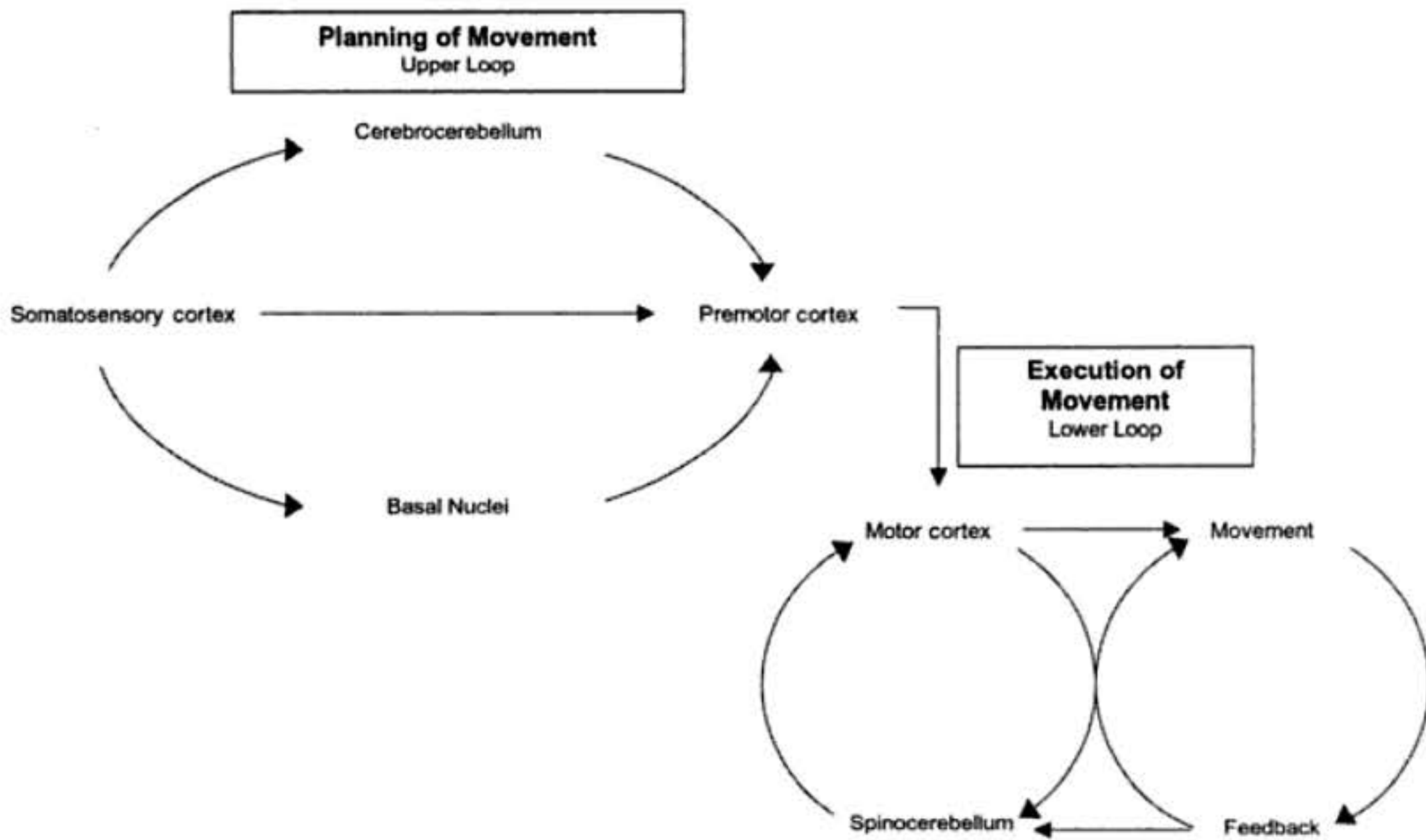


Fig. 8.6. Hypothetical map of cerebrocerebellar and spinocerebellar involvement in the planning and execution of movement.

areas of the nervous system. Therefore, a cervical lesion may affect spinocerebellar tracts and conscious proprioceptive pathways (such as cervical vertebral instability in young, large-breed dogs). Disorders of cerebellar function may result in specific alterations in motor function. These deficits may exhibit themselves as hyper- or hypometria, ataxia, dysmetria, and tremors.

It is more common for dogs and cats with cerebellar disease to exhibit signs of hypermetria. This results from the delay in the cessation of the intended movement and typically manifests itself at gait as the animal takes on a “toy soldier” appearance. The limbs are stiff and frequently overreaching. There is usually a broad-based stance and the intended movement will overshoot the goal with an excessive rebound. Ataxia can be thought of as the manifestation of a constellation of signs resulting from hypermetria, dysmetria, and asynergia. Dysmetria refers to abnormalities in the rate and force of movement. Asynergia is the lack of coordination in the execution of multisegmental movements. Since the cerebellum is usually affected in a diffuse manner, the clinical sign of ataxia is a common one. Ataxia simply refers to the “lack of an axis” or can be thought of as movement away from the axis of the body (a straight line drawn from the nose to the tail). The animals will have a broad-based stance and sway from side to side at gait. The head will often oscillate, as the vestibulocerebellar function is also affected. Affected patients tend to have difficulty maintaining their balance and are easily tipped over.

Since the spinocerebellum is somatotopically organized, a lesion of the vermis or fastigial nucleus will produce titubation. Titubation is a shaking of the trunk and head while sitting or standing, which is commonly referred to as the drunken sailor’s

gait. Tremors of cerebellar origin are referred to as intention tremors. These tremors are manifested when the animal initiates voluntary movement. They typically appear as the to-and-fro movements or oscillations of the head and neck, which become more severe as the animal begins to reach the goal (such as a food bowl). Intention tremors imply a lesion of the cerebrocerebellum; the more lateral areas of the cerebellar hemispheres or the dentate nucleus. This is the area of the cerebellum primarily influencing the application of voluntary movement. Lesions of the vestibulocerebellum (flocculonodular lobe), vestibular nuclei, or fastigial nucleus may cause nystagmus, strabismus, loss of balance, and a head tilt either toward or away from (paradoxical) the side of the lesion.

Lesions of the rostral cerebellar peduncles and deep cerebellar nuclei produce the most severe clinical signs. An abnormality in the region of the fastigial nucleus in cats may produce contralateral pupillary dilation. The affected pupil will not be completely responsive to light (miosis) and there will be partial protrusion of the ipsilateral third eyelid. With lesions of the interposital nucleus, the same pupillary light abnormalities will occur as in a fastigial nucleus lesion, however, the affected pupil is ipsilateral to the lesion.

Paradoxical vestibular syndrome and decerebellate rigidity are two classic signs of cerebellar disease. Occasionally, animals will present with a head tilt and paresis on the opposite side of the head tilt, and may or may not have other signs of cerebellar dysfunction (e.g., nystagmus or tremor). Lesions of the flocculonodular lobe or caudal cerebellar peduncles will produce these signs. In these cases the head tilt is paradoxical in that it is away from the side of the lesion. The lesion can be localized to the same side as the most severe conscious proprioceptive deficits. This paradoxical vestibular syndrome is likely due to an abnormality in the vestibulocerebellum, which contains many crossed and uncrossed pathways and, depending on the location and severity of the lesion, may result in the contralateral head tilt (see Chapter 7). Decerebellate rigidity is seen with severe cerebellar abnormalities. It is characterized by rigid extension of the forelimbs, alternating flexed or extended hind limbs, and opisthotonus. If damage is confined to the cerebellum, consciousness is maintained. The classic differentiation therefore, between an animal with decerebrate posturing and decerebellate posturing is the animal's level of consciousness. A decerebrate animal will be stuporous or comatose.

Occasionally, animals with cerebellar disease will have absent or decreased menace responses ipsilateral to the lesion. The menace deficit is produced despite normal visual pathways and facial nerve function. The cerebellum is known to play a role in the inhibition of micturition and diseases of the cerebellum may therefore play a part in disorders of micturition (see Chapter 11).

VIII. Disorders of the Cerebellum^{1-6,7,9,30,33,35-114}

A. Degenerative/anomalous

1. Cerebellar cortical abiotrophy

This group of diseases specifically refers to the degeneration of normal neuronal cell populations within the cerebellar cortex after birth. Addition-

ally, deep cerebellar nuclei and the terminal fields of cerebellar projections may be affected. Many of these diseases are genetically transmitted; most are suspected to be autosomal recessive traits. The etiology for this group of disorders is unknown. Lack of a metabolic component necessary for cellular survival may be involved. Some of these abiotrophies may represent inappropriate programmed cell death of cerebellar neurons (apoptosis).

A genetically transmitted autoimmune process was suspected in a group of young (8-wk-old) Coton de Tulear dogs with granule cell degeneration. An apoptotic process was suspected in a separate, younger (2-wk-old) group of Coton de Tulear dogs with granular cell loss. Purkinje neurons are the most commonly affected cell population in cerebellar abiotrophy cases (Fig. 8.7 and Fig. 8.8). However, granule cells, medullary nuclear cells (e.g., cuneate, gracilate, olivary nuclei), and motor neurons in the spinal cord have also been affected. Cerebellar cortical abiotrophy has been primarily reported in dogs, with only sporadic feline reports. The onset and rate of progression of clinical signs varies with the breed affected (Table 8.1). Most breeds show an onset of clinical signs when the animals begin to ambulate and slightly later (3–12 wk). The course of the disease can be rapid (several weeks) or slowly progressive (several years). In certain cases, the clinical signs will plateau and the animal will remain stable.

In some breeds, clinical manifestations of cerebellar dysfunction occur near or during adulthood. In the cerebellar abiotrophy of Gordon setters, clinical signs usually begin at about 6 to 10 mo of age and progress steadily over 9 to 18 mo. There is a late-onset cerebellar degeneration in Brittany spaniels. These dogs are typically affected between 7 and 13 yr of age. In one report of eight Brittany spaniels, the time from onset of cerebellar dysfunction to euthanasia varied from 6 mo to 4 yr. A late-onset cerebellar abiotrophy disorder has been described in Old English sheepdogs. These dogs exhibited primarily gait abnormalities (beginning between 6 and 40 mo of age) that were mild and slowly progressive. A late-onset (more than 1 yr of age) cerebellar abiotrophy has also been reported in a Siamese cat and a domestic shorthaired cat. The latter cat also exhibited retinal degeneration.

Clinical signs of cerebellar abiotrophy represent the cerebellar syndrome and may include ataxia, intention tremors, nystagmus, poor menace responses with normal vision, opisthotonus, behavioral abnormalities, and depression. Neurodiagnostics have not been beneficial in the antemortem diagnosis of this condition; however, in several breeds there are gross structural abnormalities of the cerebellum (hypoplasia) that may be detectable with magnetic resonance imaging. There are no effective treatments for this group of disorders.

2. Neuroaxonal dystrophy

This disease has been reported in dogs and cats and is characterized histologically by swellings at the terminal ends of axons referred to as “spheroids.” This is also the name of a condition secondary to the accumulation of metabolic by-products in storage diseases, where the disease results in a neuroax-

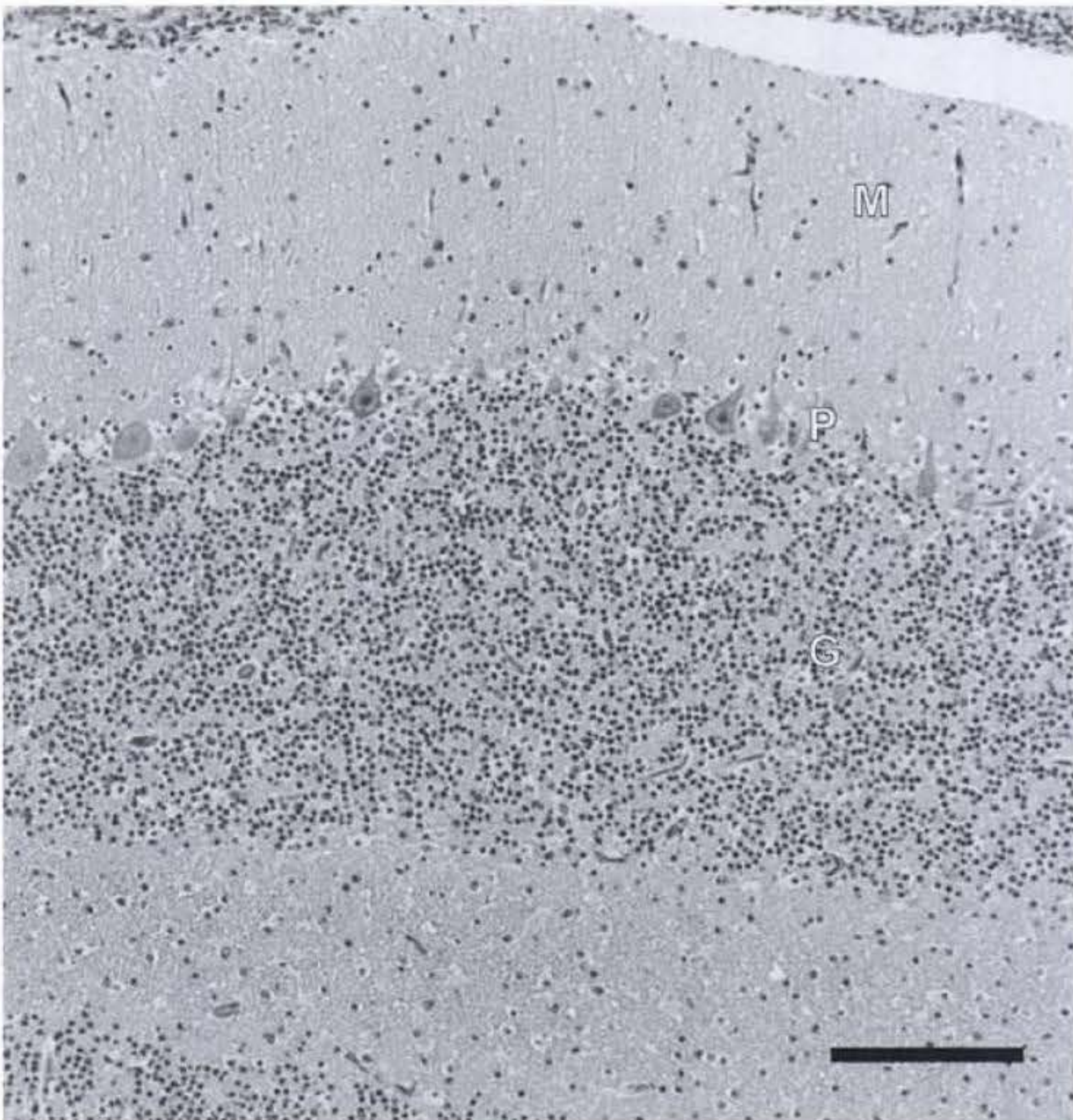


Fig. 8.7. Normal section of cerebellum. Note molecular layer (M), Purkinje cell layer (P), and granule cell layer (G). Hematoxylin and eosin stain. Bar = 200 μ m (Photograph courtesy of Kevin Lahmers, DVM, Washington State University, College of Veterinary Medicine, Department of Clinical Pathology and Microbiology).

onal dystrophy. Axons in the cerebellum and its related pathways are affected. It is thought that a defect in axonal transport leads to the accumulation of transportable products in the distal ends of the affected axons. The disease is genetically transmitted in cats and is thought to be hereditary in dogs as well. An autosomal recessive mode of inheritance is suspected. The onset of clinical signs relating to the cerebellar syndrome is typically within the first few months of life in the Chihuahua, Collie, Siamese, and domestic shorthaired cat. Boxers may be affected between 1 and 7 mo of age. The Rottweiler is

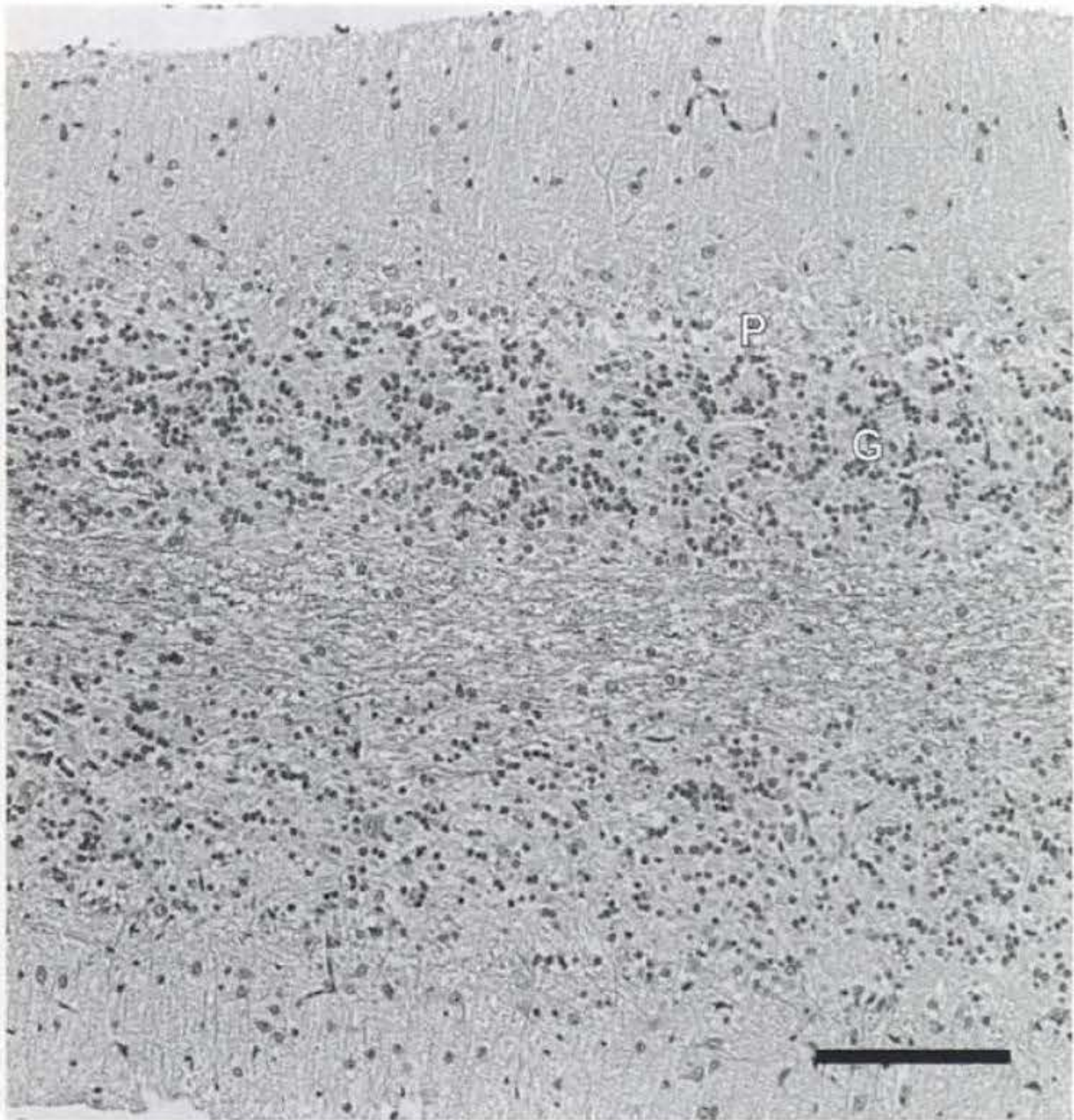


Fig. 8.8. Cerebellar abiotrophy. Notice the lack of Purkinje cells in the Purkinje cell layer (P) and thinning of the granular cell layer (G). Hematoxylin and eosin stain. Bar = 200 μ m (Photograph courtesy of Kevin Lahmers, DVM, Washington State University College of Veterinary Medicine, Department of Clinical Pathology and Microbiology).

affected within one to two years and the German shepherd may be affected at around 15 mo. In the case of the Rottweiler, there may be severe degeneration of the dorsal columns of the cervical spinal cord. These dogs often have conscious proprioceptive deficits, as well as cerebellar dysfunction. Neuroaxonal dystrophy is usually slowly progressive and there is no treatment.

3. Cerebellar malformation

It is thought that a genetically transmitted condition of cerebellar hypoplasia exists. This condition has been reported in a Chow Chow, Boston

Table 8.1: Breeds of Dogs and Cats Recognized to Have Cerebellar Abiotrophy

Breed	Age of onset	Rate of progression
Dogs		
Airedale Terrier	< 6 months	Progressive
Australian Kelpie	6–12 weeks	Progressive
Beagle	3 weeks	Progressive
Bernese Mountain Dog	4–6 weeks	Progressive
Border Collie	6–8 weeks	Progressive
Brittany Spaniel	7–13 years	Slowly progressive
Bull Mastiff	4–28 weeks	Progressive
Coton de Tulear	8 weeks/2 weeks	Progressive/non-progressive ¹
Finnish Harrier	< 6 months	Progressive
Gordon Setter	6–30 months	Slowly progressive
Irish Setter	3–10 days	Progressive
Jack Russell Terrier	2 weeks	Progressive
Kerry Blue Terrier	8–16 weeks	Progressive
Labrador Retriever	12 weeks	Rapidly progressive
Miniature Poodle	3–4 weeks	Unknown
Old English Sheepdog	6–40 months	Slowly progressive
Rhodesian Ridgeback	Birth	Progressive
Rough Coated Collie	4–8 weeks	May stabilize
Samoyed	Birth–6 months	Slowly progressive
Cats		
Siamese	> 1 year	Slowly progressive
Domestic Shorthair	> 1 year	Slowly progressive
Mixed Breed	6–8 weeks	Progressive

Note: Isolated cases have been reported for German Shepherd, English Springer Spaniel, Pit Bull Terrier, Portuguese Podenco, Golden Retriever, Cocker Spaniel, Cairn Terrier, Great Dane, Akita, Clumber Spaniel, Fox Terrier, Scottish Terrier, Mixed Breed.

¹There are two forms of abiotrophy reported in this breed; one appears to be progressive and the other is nonprogressive.

terrier, Airedale terrier, Irish setter, Wire-haired Fox terriers, and Bull terrier. The reported malformations vary from complete absence of the cerebellum or parts of the cerebellum (agenesis), abnormal development of the cerebellum with no differentiation of tissue (aplasia), and abnormal development of the cerebellum with some differentiation of tissue (hypoplasia). The condition is present at birth and likely represents failure of normal cerebellar development. The condition is not progressive and clinical signs may improve as the animal matures.

4. Dandy-Walker syndrome

This is a rare congenital malformation that shares similarities with the human form of the disease. It consists of a triad of congenital anomalies,

which include cerebellar vermian hypoplasia, a communicating hydrocephalus, and the presence of a fluid-filled cyst (syrinx) within the posterior fossa. It has been reported in several dogs with no breed or sex predilection and in a kitten. The clinical signs are typical of cerebellar disease (ataxia, hypermetria, absent menace, and tremors). Some dogs have also displayed a head tilt and circling. It is unknown if the vestibular signs are due to the cerebellar disease or manifestations of the other developmental abnormalities. The clinical signs are typically not progressive, therefore surgical intervention may not be rewarding. The condition has been reported in one kitten. Affected animals usually present early in life around three months of age. There is no treatment.

5. Foramen magnum-associated malformations

Malformation of the caudal aspect of the skull, similar to Chiari Type I disorder of people, has been described in small-breed dogs. These *Chiari-like malformations* are best appreciated on sagittal MR images and usually include rostral displacement of the caudal aspect of the occipital bone, with caudal displacement of the caudoventral aspect of the cerebellum into or through the foramen magnum. There may be meningeal fibrosis at the cervicomedullary junction in dogs with Chiari-like malformations. Overcrowding of the caudal fossa region is believed to lead to hydromyelia/syringomyelia, especially in the cervical spinal cord region. Concurrent hydrocephalus may also be present. Some patients with Chiari-like malformations may display evidence of cerebellovestibular dysfunction. Medical therapy (e.g., low doses of prednisone) may be successful in some cases of Chiari-like malformations. Foramen magnum decompression (FMD) is usually successful in people with the disorder, and the authors have had some success in dogs treated similarly. Chiari-like malformations are also discussed in Chapter 9.

Occipital dysplasia is a controversial anatomical abnormality of the occipital bone. This condition also primarily affects small-breed dogs. In cases of occipital dysplasia, the region of the occipital bone comprising the dorsal boundary of the foramen magnum is malformed and replaced by a membranous band of tissue. Oftentimes, the caudal aspect of the cerebellum and the dorsal aspect of the cranial cervical spinal cord–caudal brain stem are exposed. It has been proposed that fluid-filled cavities in the brain stem and cranial cervical spinal cord, seen on MR examination of dogs with this condition, are secondary to abnormal pulsation of cerebrospinal fluid through the foramen magnum. The authors have surgically removed this band of tissue in several dogs and have seen an improvement in clinical signs relating to ataxia and cerebellovestibular disease.

B. Neoplasia

1. Primary brain tumors

Numerous primary neoplasms can affect the cerebellum. Typically, adjacent structures such as the brain stem and associated cranial nerves are

affected as well. Not all neoplastic process may be histologically considered invasive or malignant; however, because of the limited space for expansion they are not considered to be benign, from a clinical point of view. Meningiomas are the most common brain tumor of dogs and cats. Unlike the meningiomas of humans and cats, dog meningiomas tend to be invasive to surrounding tissue and therefore difficult to entirely remove surgically. They usually form at the cerebellopontine or cerebellomedullary junction and grow toward the path of least resistance, which is usually into the fourth ventricle. For this reason they can be mistaken for choroid plexus tumors, which arise from the ventricles. They may also arise from the dural covering adjacent to the tentorium cerebelli. Advanced imaging techniques such as CT or MRI are necessary to aid in accurate diagnosis. The CT and MR features of meningiomas have been described (see Chapter 4). Briefly, they are strongly contrast-enhancing, well-circumscribed masses that arise from the covering of the brain and, therefore, have a broad-based appearance (Fig. 8.9). There can often be thickening of the bone adjacent to the tumor (hyperostosis). Choroid plexus tumors are also strongly contrast-enhancing; however, these tumors lack the broad-based appearance of meningiomas. Cystic meningiomas have been reported in the dog. A broad-based, contrast-enhancing rim of tissue, filled with fluid, characterizes these tumors. Feline intracranial meningiomas are benign growths, in that they do not invade surrounding tissue. They are usually well encapsulated and therefore good candidates for surgical resection. When meningiomas extend into the fourth ventricle they can be more difficult to remove.

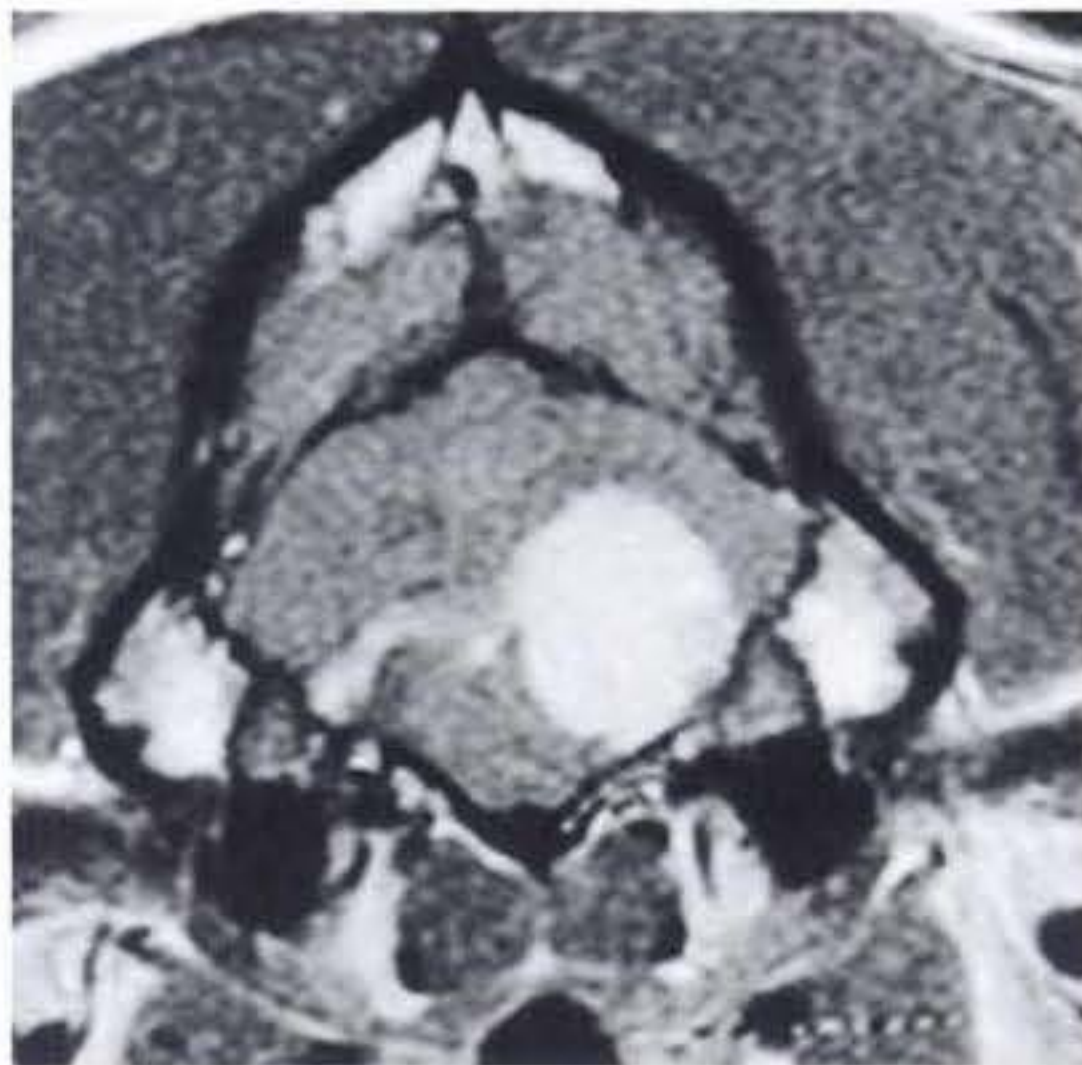


Fig. 8.9. Transaxial MR image of a dog's brain, demonstrating a large, contrast-enhancing cerebellomedullary mass.

Gliomas are neoplasms that originate from the supporting cells of the central nervous system (astrocytes and oligodendrocytes). Astrocytomas may be benign or malignant histologically; however, their presence in a confined space (the caudal fossa) compresses surrounding brain structures. They are usually slow growing, have poorly defined margins, and have a heterogeneously contrast-enhancing pattern that may also have ring enhancement. Oligodendrogliomas are round-cell tumors that invade surrounding tissue and are highly destructive. The incidence of gliomas is greatest in brachycephalic dogs.

Choroid plexus tumors and ependymal tumors arise within the ventricles. These tissues are related embryologically and function in the production and movement of cerebrospinal fluid. Tumors of ependymal origin are rare. The fourth ventricle is a common site for choroid plexus tumors. The choroid plexus is a very vascular tissue and therefore strongly contrast enhances on MR examination. Both of these tumor types can shed cells into the normal CSF pathways and therefore a multifocal neuroanatomic localization is possible. Metastases of these tumors via cerebrospinal fluid pathways are referred to as “drop” metastases (“drop mets”).

Medulloblastomas are highly metastatic brain tumors, typically occurring in the cerebellum of dogs and cats, usually between 3 and 10 yr of age. These tumors share many characteristics with the same tumor type in people. They are classified as a primitive neuroectodermal tumor. They arise from a population of cells thought to be present during the development of the cerebellum. Animals may present early or later in life with signs of cerebellar disease and possibly signs of brain-stem compression. As the tumors grow into the fourth ventricle, they will often cause obstructive hydrocephalus. Tumor cells will invade the adjacent meninges. Metastasis along CSF pathways is also common.

Epidermoid cysts are structural abnormalities that may result in cerebellar dysfunction. These masses of tissue are not technically classified as neoplasia; however, because of their location, they create similar clinical signs. It is thought that they arise from an embryological invagination of neuroectoderm. During embryological development, portions of ectoderm destined to become skin, become entrapped in the closing neural tube. Because the neural canal closes from a caudal to cranial direction, the fourth ventricle and cerebellomedullary junction is a common site for these abnormalities. They are present at birth; however, the onset of clinical signs usually occurs later in life. Because they are invaginations of tissue destined to become skin, they are filled with keratin and desquamated epithelial cells. They cause cerebellar signs due to the slow compression of surrounding structures.

2. Secondary brain tumors

The central nervous system is a common site of metastatic tumors. The cerebellum may be affected through hematogenous spread or spread through the CSF pathways. The extent and nature of cerebellar dysfunction will be

referable to the site of the metastatic tumor (i.e., it may involve other surrounding structures). Common metastatic tumors include mammary adenocarcinoma, prostatic adenocarcinoma, pancreatic adenocarcinoma, pulmonary adenocarcinoma, melanoma, hemangiosarcoma, and lymphoma.

Tumors of surrounding structures of the central nervous system may also compress the cerebellum. These include tumors of the skull, such as osteosarcoma, chondrosarcoma, and multilobular osteochondrosarcoma.

C. Infectious/inflammatory

1. Feline panleukopenia (Parvovirus)

One of the most well-recognized disorders of cerebellar development is the in-utero infection of feline embryos with the feline panleukopenia virus (FPV). Kittens infected with FPV either in utero or in the perinatal period may develop cerebellar dysfunction secondary to cerebellar hypoplasia. Infections resulting in clinical signs of cerebellar disease cause inflammation of the brain and destruction of cells in the external germinal layer of the cerebellum. This layer is highly active prior to and in the first few weeks following birth. This active division leads to the fully functional cerebellum. Disruption of the division of these cells leads to hypoplasia of the granule cell layer and gross cerebellar hypoplasia. Purkinje cells that are actively growing may also be affected. Kittens typically present with a nonprogressive, symmetric cerebellar ataxia usually noticed at the onset of ambulation. Occasionally, other areas of the central nervous system will be affected. With time, most cats will compensate for the cerebellar dysfunction and clinical signs may abate.

2. Canine herpes virus

The predilection of clinical signs related to cerebellar dysfunction secondary to viral infection is likely due to the developmental nature of the tissue affected. The Purkinje neurons in the cerebellum are exquisitely susceptible to all types of injury. This, when considered with the fact that the granule cell layer is continuing to develop well into the perinatal time period, provides a plausible explanation as to why clinical signs of cerebellar disease would predominate. Puppies exposed to canine herpes virus either in utero, during parturition, or within the first two weeks of life can develop a herpes virus meningoencephalitis that can preferentially affect the cerebellum. Nearly all puppies with an active infection early in life will succumb to the infection. However, a few will live and have residual lesions in the central nervous system. Although other organs may be affected (lung, kidney, and liver), signs of a cerebellar syndrome in a newborn puppy would indicate that a herpes virus infection is a likely differential diagnosis. Surviving puppies may also be affected with retinal dysplasia, as this tissue is also undergoing active differentiation at the time of the infection.

3. Canine distemper virus

Canine distemper virus may affect dogs of any age, however, there is a pattern to the destruction of nervous system tissue that is age dependent.

Those dogs affected with the disease early in life suffer from a polioencephalomyelopathy (gray matter disease), usually have a history of seizures, and rarely survive. Dogs affected by the disease later in life may have brainstem, cerebellar, and vestibular signs. They typically have a leukoencephalomyelopathy (white matter disease) or a combination of gray and white matter disease and in most cases the disease is less severe. The cerebellar peduncles are commonly affected, however, distemper virus can affect all segments of the nervous system. A common sequela of an infection with canine distemper virus is a rhythmic myoclonus of a single muscle group that may be mistaken for tremors.

4. Feline infectious peritonitis (FIP)

The pyogranulomatous (dry) form of feline infectious peritonitis virus can affect the central nervous system and may result in inflammation of the ependyma, choroid plexus, or meninges that surround the brain stem and junction of the cerebellum and medulla. This disease can be a challenge to diagnose, as definitive antemortem tests to prove a cat has the disease are virtually nonexistent. In a recent report, however, it was found that a high CSF IgG titer against feline coronavirus (greater than 1:25) was predictive of FIP as a causative entity. It has been reported that over 45% of cats affected with the dry form of the disease will have signs of central nervous system dysfunction. This results from an inflammatory response to the virus and a lack of a protective cell-mediated immune response. Because the disease occurs as a multifocal pyogranulomatous meningoencephalomyelitis in the central nervous system, the neuroanatomic localization can be diverse. Various guidelines have been suggested for the clinician to follow in order to make a presumptive diagnosis. They include history of possible exposure, clinical signs, high CSF coronaviral titers, and concurrent infection with feline leukemia virus. The disease is usually fatal except in rare cases.

5. Granulomatous meningoencephalomyelitis (GME)

Granulomatous meningoencephalitis has been reported as primarily affecting the cerebellum; however, the condition typically affects multiple areas of the central nervous system. Three forms of the disease have been described: the disseminated (multifocal) form, the focal form, and the ocular form. The disseminated form usually has a much more rapid onset and progression than the focal form. This disease is typically characterized by a massive perivascular inflammatory response consisting of histiocytes, plasma cells, and lymphocytes, occasionally mixed with other leukocytes. It primarily affects the white matter, but can affect the gray matter as well. The condition most commonly affects young (1–3-yr-old), small-breed dogs and has a higher incidence in females than males. Lesions in the region of the cerebellomedullary angle are common. Affected animals will present with clinical signs referable to structural disease of the cerebellum (i.e., ataxia, tremors, nystagmus). The extensive accumulations of inflammatory cells are at times so proliferative that they compress surrounding tissue. Treatment of GME is

problematic (see Chapter 4). Corticosteroid therapy may relieve clinical signs, but this is often for a short period of time (weeks to months). When the histiocytes are admixed with inflammatory cells, the distinction is one of a non-suppurative meningoencephalomyelitis. If histiocytes are the predominant monomorphic form, then the classification is more akin to neoplasia. It has been suggested that the nonsuppurative form of the disease may be a form of neoplasia as well. Because the predominant cell types appear to originate from the monocyte-macrophage cell lines, radiation therapy has been proposed and has been utilized successfully in the treatment of focal GME.

6. Fungal diseases

All of the commonly encountered mycotic organisms may infect the central nervous system; however, the most frequently seen infections are *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. They typically result in a diffuse or multifocal meningoencephalitis. The central nervous system may be infected through systemic dissemination (i.e., hematogenously), local extension (e.g., nasal, frontal sinuses), migrating foreign bodies (e.g., grass awns), or surgical procedure (iatrogenically). Central nervous system infections may involve the junction of the cerebellum and the medulla resulting in cerebellar, vestibular, and other brain-stem signs. Additionally, because of the typical multifocal presentation of these infections, signs of cerebral and spinal cord involvement may be apparent along with cerebellar signs. Fluconazole is the treatment of choice. Additional information regarding CNS fungal infections can be found in Chapter 4.

7. Rickettsial disease

The vasculitis caused by either Rocky Mountain spotted fever or ehrlichiosis may cause a meningoencephalitis in dogs. Dogs neurologically infected with a rickettsial disease commonly present with vestibular dysfunction, usually after a history of lethargy, depression, and fever. The hematologic abnormalities secondary to a rickettsial infection or vasculitis may pass without the owners being aware that the animal was infected. Cerebellovestibular signs may be appreciated in combination with clinical signs referable to other areas of involvement in the central nervous system. Rickettsial diseases are rare in cats. Additional information regarding CNS rickettsial infections can be found in Chapter 4.

8. Protozoal disease

The nervous system of both dogs and cats may be infected by the coccidian protozoan *Toxoplasma gondii*. *Neosporium caninum*, a protozoal organism related to *Toxoplasma* is known to naturally infect the nervous system of dogs only. These infections typically present as multifocal disease and are supported by systemic illness. They can infect animals of all ages and breeds. Immunocompromised or immunosuppressed animals are more susceptible to infection. The infections cause necrosis and a nonsuppurative encephalomyelitis of both gray and white matter. Infectious foci can form granulomas, which may result in signs consistent with focal disease. Clinical signs of cerebellovestibular disease would be expected if the lesion caused

compression or inflammation of the cerebellum, cerebellar peduncles, or brain stem.

Additional information regarding CNS protozoal infections can be found in Chapter 4.

9. Algal disease

Prototheca wickerhamii and *Prototheca zopfii* are species of ubiquitous algae that have been reported to cause central nervous system disease. The disease is rare and it is thought that an abnormality of the animal's immune system must contribute to the pathogenesis of the infection. Animals will present with systemic signs of illness and multifocal neurologic disease, the clinical signs of which will be dependent upon the area of the nervous system affected. The pyogranulomatous lesions seen in the brains of dogs with protothecosis may cause signs of cerebellovestibular dysfunction. In one case, an *eosinophilic* pleocytosis was reported. The organism has a predilection for the eyes, so ocular changes may accompany signs of multifocal neurologic disease.

D. Trauma

Trauma to the brain is discussed in detail in Chapter 5. Trauma involving the cerebellum is uncommon due to the fact that the cerebellum is in a particularly isolated environment. It is almost completely surrounded by bone. Dense bone surrounds three-fifths of the cerebellum as the cranial vault at the caudal, lateral, and dorsal aspects. The rostral aspect of the cerebellum is separated from the cerebrum by the partially osseous tentorium (tentorium cerebelli). Additionally, in dogs, there is a large mass of muscle that surrounds the caudal skull.

Trauma to the cerebellum may be divided into primary injuries such as skull fractures, blood vessel damage and tearing/crushing of the cerebellar parenchyma, and secondary injuries that are a result of physiological changes, such as increased intracranial pressure, ongoing hemorrhage, ischemia, and cerebellar edema. In the second class of injuries are the injuries that may benefit from medical or surgical therapy. Primary cerebellar injuries are irreversible. Of major concern is the decrease in cerebellar perfusion secondary to increased intracranial pressure. The Purkinje cells of the cerebellum are exquisitely sensitive to ischemic, as well as compressive (edema) injury. There are two types of edema associated with cerebellar injury. Cytotoxic edema results from the failure of membrane transport systems in the cell secondary to a decreased production of ATP. Decreased ATP production is due, in turn, to hypoxia and disruption of the electron transport chain. This cascade of events eventually leads to accumulation of water and solute in the cells themselves. Vasogenic edema results from the damage to membranes secondary to free radical production and lipid peroxidation. These damaged membranes then leak protein and other small solutes into the interstitial space. In general, vasogenic edema is more responsive to medical therapy than cytotoxic edema.

Corticosteroid therapy is a focus of great controversy in the treatment of brain trauma. The Brain Trauma Foundation does not recommend the use of glucocorticoids in people. There is conclusive evidence that the use of glucocorticoids does not lower intracranial pressure or improve the outcome of humans with severe

head injuries. The beneficial effects of corticosteroids in the treatment of brain trauma may be limited to their ability to treat vasogenic edema (edema most commonly associated with brain tumors and other masses). Unfortunately, the major edema associated with brain trauma is cytotoxic. The basics of treatment for brain trauma include adequate fluid resuscitation and support, oxygenation and ventilation, mannitol, nutritional support, supportive care (e.g., eye lubrication, padded surface, rotation), adjunctive treatment (moderate hypothermia, free radical scavengers, etc.), and surgery, if necessary. The pathophysiology of brain trauma is very complex. Additional information concerning brain trauma can be found in Chapter 5.

E. Miscellaneous causes of cerebellar disease

1. Lysosomal storage diseases

Lysosomal storage diseases of the central nervous system represent a group of disorders which have in common the accumulation of metabolic by-products within the perikaryon, axon, dendrites, or surrounding neuropil. Storage diseases can primarily affect the cerebellum, however, they usually are very diffuse in their localization, affecting multiple areas of the brain and spinal cord. Animals with lysosomal storage diseases affecting the cerebellum will typically present at a young age, due to the fact that these diseases are congenital. However, there are few reports of animals presenting with signs of cerebellar disease later in life. Numerous storage diseases may have the potential to affect the cerebellum. A few of the more commonly documented diseases are discussed here. More information concerning lysosomal storage diseases is provided in Chapter 4.

Lafora bodies are polyglucosan deposits within the central nervous system. They have been associated with disease of the central nervous system in various small animals including a 4.5-yr-old cat that presented for head-bobbing and whole-body tremors. The Lafora bodies were most numerous in the granule cell layer of the cerebellum and in Purkinje neurons. Neuronal ceroid-lipofuscinosis has been most commonly reported in the dog. A similar condition affects cats. The disease results from intraneuronal accumulations of ceroid-lipofuscin granules. It has been related to primary cerebellar disease in the dog. It can result in gross cerebellar atrophy. Dogs with this storage disease will usually present at less than 1 yr old; however, they may not show clinical signs until they mature. Niemann–Pick disease type C in the cat causes neurologic deterioration and hepatosplenomegaly. This disease is caused by an accumulation of sphingomyelin and other lipids in the central nervous system and reticuloendothelial tissues (e.g., spleen, liver). Neuroaxonal dystrophy is the primary histologic feature of the disease. Cats affected by this disease will usually show signs of tremor by 8–12 weeks. The disease will slowly progress until the cat is unable to stand. Eventually, the menace responses may disappear as well. In people, those children who have the late infantile form (3–5 yr old) have primarily cerebellar signs. Although these

storage diseases are rare, they should be suspected in young animals that present with slowly progressing cerebellar signs.

2. Ischemic/vascular

Because of the cerebellum's sensitivity to ischemic changes secondary to hypoxia, clinical signs of cerebellar disease may be evident before signs related to other areas of the brain following ischemic events. A definitive antemortem diagnosis of cerebellar infarct is usually not possible. With advanced imaging techniques such as MR (Fig. 8.10), however, a presumptive diagnosis can usually be made by combining imaging results with history, signalment, and results of ancillary diagnostic tests. Clinical signs of cerebellar disease will be ipsilateral to the area damaged in the cerebellum. If the damage to the cerebellum is minor, one would expect the animal to have a good prognosis, with typical improvement in clinical status seen within the initial 72 hr after the

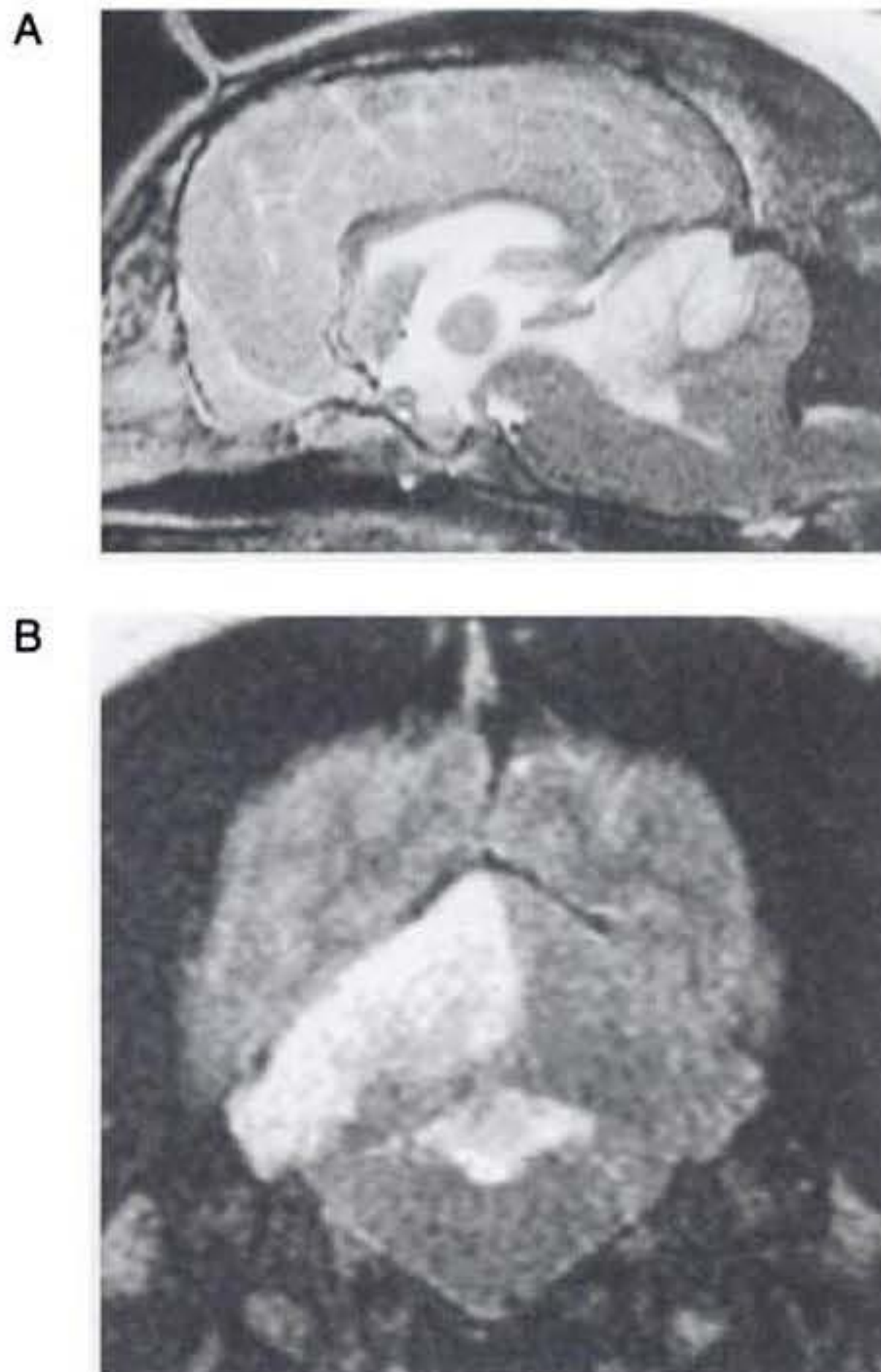


Fig. 8.10. T2-weighted sagittal (A) and transaxial (B) MR brain images from a dog with a cerebellar infarct.

ischemic episode. Causes of thromboembolic disease such as hyperadrenocorticism, hypothyroidism (atherosclerosis), bacterial endocarditis, heartworm disease, hyperlipidemia, and neoplasia must be ruled out as potential causes. Ischemic/vascular encephalopathy is also discussed in Chapter 4.

TREMOR SYNDROMES¹¹⁴⁻¹³⁴

I. Pathophysiology and Classification

Tremors in dogs and cats can be caused by a variety of conditions affecting the nervous system. A tremor is an involuntary, rapid, back-and-forth movement of a body part that is found in both normal and abnormal animals. Much of the understanding of the pathophysiology of tremor in humans has been elucidated in the last 15 yr. It is important to remember that many of the experiments that have generated the current conclusions regarding the pathophysiology of tremors in people were performed on animals. It is difficult to categorize tremors of dogs and cats in the same groupings as human tremors. In people, tremors are characterized by their frequency in Hz (or cycles per second), the location of the tremor (e.g., fingers, legs, head, etc.), and the condition in which the tremor occurs (e.g., at rest, standing, goal-oriented behavior, etc.). The origins of tremors are uncertain. The activity of the brain is intensely rhythmic. Oscillators are systems that have the ability to produce rhythmic activity. These are not necessarily discrete anatomic structures. They may likely be neural circuits or connections between subsystems that have an inherent ability to function in this manner. Neurons have the ability to resonate and set up oscillatory firing. The subcortical oscillations of neurons occur through electrical coupling via gap junctions. These neurons resonate at 7–10 Hz, which is the typical range for physiologic tremors.

The basic modes of tremor genesis in humans include (1) *mechanical tremor*—tremor due to the resonance frequency of the activated muscle, which can be changed based on the load against the muscle; (2) *reflexes of the central nervous system*—tremor due to the alternating antagonistic flexion/extension of muscles. For example, when a limb is extended, there are impulses that allow the antagonistic muscle to cause flexion. Conversely, as that muscle is flexing, impulses are generated to allow the antagonistic muscle of that activity to cause extension (this is a component of fluidity of movement). The muscles will have synchronized frequency peaks that are equivalent to the frequency of the portion of the limb that generates that movement; (3) *central oscillation*—either the rhythmic activity of a group of neurons in a nucleus (the electro-tonic coupling of oscillatory activity through gap junctions), or through oscillations created by neural circuits between different nuclei or different populations of neurons; (4) *malfunction of feedforward loops*—This occurs within the central nervous system and most commonly in the cerebellum. It is commonly recognized as intention tremor. In this case, a deficit of cerebellar function causes a delay of the antagonistic movement, which results in a decreased braking of a ballistic movement and an overshoot movement. Compensation then leads to a correction movement, which causes hypermetria in the opposite direction. Eventually the abnormality will create an oscillatory movement that is intensified during goal-oriented behavior.

The following will be a classification of tremors in animals based on current human classifications, realizing that certain descriptive aspects and therefore classifications are not possible in animals. By excluding possible categories of tremors based solely on anthropomorphism (e.g., psychogenic tremors) or lack of reported occurrence in animals (e.g., Parkinsonian tremors), we may limit the future identification of animal models of tremors. Therefore, although specific examples of tremors in animals that are recognized in humans may not be discussed (because we have not documented them), the categories will be mentioned nonetheless. Tremors can be divided into two broad categories: physiologic tremors and pathologic tremors. Pathologic tremors are those that impair motor function. Physiologic tremors are present in normal animals at a low-amplitude movement that is difficult to discern with the naked eye. There are three components to a physiological tremor. The mechanical component is due to the passive properties of cardiac activity during systole, referred to as the *ballistocardiogram*. The mechanical component may be augmented by sympathetic reflexes (e.g., epinephrine enhancement of muscle spindle activation). Finally, a central component is hypothesized, wherein synchronization of motor neurons by the brain is responsible for the amplification of the tremor. These tremors can occur at rest or with posture. A group of physiologic tremors that are looked at as “physiological tremor of pathological amplitude” is known as *enhanced physiological tremor*. These tremors are an exaggeration of the normal physiological tremor and may be caused by metabolic abnormalities (electrolyte disturbances, hypoglycemia, etc.), stress, exercise, certain medications (e.g., metoclopramide, diphenhydramine, etc.), and toxins (e.g., lead, organophosphates, etc.).

The pathologic tremors consist of cerebellar tremors, Parkinsonian tremors, rubral tremors, tremors due to peripheral neuropathy, dystonic tremors, palatal tremors, orthostatic tremor, and psychogenic tremors. Cerebellar tremors (intention tremors) were discussed previously and may result from any pathology that affects cerebellar function. They have been associated with lesions involving the lateral cerebellar hemispheres, the vermis, and the interposital nucleus. These tremors will be bilaterally symmetric if due to a toxin or degenerative condition that affects the cerebellum and ipsilateral to specific lesions of the cerebellum such as an infarct or neoplasia. Cerebellar tremors can be presumed when there are other signs of cerebellar dysfunction (e.g., ataxia, nystagmus). Parkinsonian tremors are specifically due to an abnormality in the synthesis of the neurotransmitter dopamine. These tremors are due to alterations in the circuitry of the basal nuclei motor loop. Dopamine plays a very important role in the proper function of this motor loop. In Parkinson's disease there is degeneration of the substantia nigra. The substantia nigra is a group of cells in the midbrain responsible for the synthesis of dopamine. Terminal fields of the substantia nigra are located in the caudate nucleus and globus pallidus, where dopamine exerts some of its major effects. This degeneration of the *nigrostriatal* pathway is also seen in horses that ingest the toxic weeds, yellow star thistle (*Centaurea solstitialis*), and Russian knapweed (*Centaurea repans*). This particular type of tremor has not been recognized in dogs or cats.

Holmes's tremor (formerly known as rubral or midbrain tremor) is a tremor that is a combination of cerebellar tremor and basal nuclei tremors. They may result from

lesions in the cerebellum/midbrain and thalamus. These tremors have an erratic, uneven appearance with a relatively low frequency (less than 4.5 Hz). They are often the result of lesions of the cerebellar outflow pathways. In people, there is a delay between lesion onset and activation of the tremor of 4 wk to 2 yr.

Peripheral neuropathies, especially those resulting in demyelination, may cause tremors. These can have an insidious onset and may result from congenital, inherited, metabolic, toxic, and inflammatory etiologies. Dystonic tremors involve muscles affected by abnormal muscle tone; however, it is thought that the origination of the tremor in people is in the basal nuclei. These tremors are typically focal, high-frequency (less than 7 Hz), and inconsistent amplitude. A rhythmic oscillation of the soft palate in people is a rare condition known as palatal tremor. This condition is known to occur with abnormalities of the inferior (caudal) olivary nucleus. It develops secondary to lesions in the cerebello-olivary projection from the cerebellum to the contralateral olivary nucleus via the superior (rostral) cerebellar peduncle. The lesion causes a disinhibition of the inferior (caudal) olive neurons, which become electronically coupled via gap junctions. It has not been recognized in dogs or cats. Orthostatic tremor is reported in people as a sensation of unsteadiness or quivering when standing up. This tremor is a fine tremor (approximately 13–18 Hz) of the legs and is only apparent when standing. It is hypothesized that this tremor disorder originates from the brain stem in a center responsible for regulating stance or muscle tone. There is an animal model of this disorder in pigs. It has not been recognized in dogs or cats.

In people, several criteria must be met before a diagnosis of psychogenic tremor can be made. Essentially it is a tremor generated as voluntary movement that requires little attention to be maintained. The tremor may be associated with clonus of the affected body part. The amplitude of a hand tremor will usually decrease when a load (weight) is applied to the hand. With psychogenic tremor, the amplitude of the tremor increases when a load is applied. This is interpreted as necessary co-activation of the muscles in order to maintain the reflex activity that generates the tremor. Other clinical signs of psychogenic tremor in people include a history of somatization, which is multiple physical complaints that suggest a physical disorder without any physical impairment to account for them; the sudden onset of the condition or remission of the condition; other unrelated neurologic signs; a decrease in the tremor amplitude or frequency when the subject is distracted or performing movements of the contralateral hand. Obviously, from this description, it is unlikely that this tremor disorder exists in animals. Many of the tremor classifications described above have not been recognized in animals. It is hoped that with a better understanding of tremor disorders (through those documented in humans), we may better recognize the abnormalities in animals. Based on frequency and circumstance (resting, posture, or intention), a general neuroanatomic localization may be made.

II. Tremor Disorders in Dogs and Cats

A. Hypomyelination/dysmyelination (dysmyelinogenesis)

Congenital tremors due to hypomyelination or dysmyelination have been reported in many breeds of dogs, and rarely in the cat. The condition is known to affect the Chow Chow, Weimaraner, Bernese Mountain dog, Samoyed, Springer spaniel, Dalmatian, Lurcher dog, mixed breeds, and the Siamese cat. In the majority of congenital tremor syndromes attributable to disorders of myelin formation, the defect is confined to the central nervous system. Peripheral nerves are unaffected. This discrepancy most likely arises from the difference in the cells responsible for myelination in the central and peripheral nervous systems. Oligodendrocytes are responsible for the myelination of many axons within the brain and spinal cord. Once the axons leave the central nervous system, the Schwann cell takes over the responsibility of myelination; however, a single Schwann cell will only myelinate a single axon. Dysmyelination, strictly defined, refers to decreased myelination due to an abnormality of the myelin itself. Hypomyelination implies that the myelin is biochemically normal but present in decreased amounts. In almost all cases studied, the clinical signs appear within the first several weeks of age; however, cases of delayed onset have also been described.

In the recessive X-linked hypomyelination disorder of Springer spaniel dogs ("shaking pups"), a severe generalized tremor is first appreciated in the second week of life in affected male dogs. These dogs are unable to stand or walk, and do not improve over time. Female carriers of the defective gene may display a mild generalized tremor during the second week of life, which resolves by 4–6 wk of age. Dogs with this disorder may develop seizure activity as they mature. The Samoyed breed is affected with a hypomyelination disorder very similar to that of the Springer spaniel dogs. Other breeds with hypomyelination/dysmyelination disorders tend to have less-severe clinical syndromes, in comparison with Springer spaniels and Samoyeds. In these breeds, the disorder is suspected to be inherited as an autosomal recessive trait, with incomplete penetrance. Clinical signs of dysfunction often plateau between 6 and 8 mo in these animals, and then gradually dissipate. The tremoring resolves in many such cases at approximately 1 yr of age.

In general, patients with hypomyelination/dysmyelination will often have a resting or intentional tremor that worsens with excitement and exercise and resolves with sleep, a "rocking horse" stance, and a bunny-hopping gait when ambulating (in those dogs able to do so). Histologically, the abnormalities appear to have a somewhat consistent involvement of the ventral and lateral columns of the spinal cord white matter. In some cases, there are normal numbers of oligodendrocytes, and in others there are altered ratios of oligodendrocytes and astrocytes. The astrocytosis may be a reaction to the degeneration of oligodendrocytes, or the functional cause of the myelin abnormality. Numerous hypotheses have been postulated as to the cause of the disorder. These hypotheses include abnormal stem cell migration, abnormal glial cell differentiation, defects in oligodendrocyte metabolism, and alterations in the genetic code (mutations) responsible for proteins required for normal oligodendrocyte or myelin function. The etiology is likely different for each separate clinical syndrome. Most current research is focusing on specific proteins necessary for the normal architectural stability of

myelin and terminal differentiation of oligodendrocytes. It is important to remember when presented with an animal that is suspected of a congenital tremor syndrome, that numerous etiologies may account for the disorder: these include infectious/inflammatory agents, inherent abnormalities of metabolism, or genetic mutation. Animals affected with congenital hypomyelination or dysmyelination may improve with age and lead acceptable lives.

B. Central axonopathy of Scottish terriers

A tremor syndrome has been described in three Scottish terrier puppies. The etiology of this disorder is unknown. Axonal loss was evident throughout the CNS upon histopathologic examination. The affected dogs developed severe generalized tremors and ataxia at 10–12 wk of age. Two of the three dogs were paraparetic. The clinical signs worsened with exercise and excitement, and abated with rest or sleep. The disorder is felt to be progressive and is associated with a poor prognosis.

C. Corticosteroid responsive tremor syndrome (CRTS)

This is a well-recognized, fairly common disorder. Although white dogs (e.g., Maltese, West Highland White terrier) appear to be overrepresented, the term “white shaker dog” syndrome is misleading. Approximately one-half of dogs with CRTS do not have white coat coloring. Most dogs affected with this generalized tremor syndrome are young (less than 5 yr old) and most are less than 15 kg. The prevailing clinical sign of dysfunction in CRTS is a fine, whole-body tremor; other reported signs of neurologic dysfunction include decreased menace responses, head tilt, nystagmus, paraparesis, tetraparesis, ataxia, and seizure activity. Dogs with CRTS occasionally have slightly elevated rectal temperatures. The tremors are rarely incapacitating and nearly all affected dogs respond to immunosuppressive dosages of corticosteroids. In one report, 80% of affected dogs responded to immunosuppressive corticosteroid therapy within three days. The condition can be separated from other inflammatory causes on the basis of CSF examination. This syndrome is characterized by a minimal to moderate nonsuppurative (i.e., lymphocytic) pleocytosis, in contrast to the polymorphonuclear pleocytosis associated with mycotic and bacterial infections and the mixed-cell pleocytosis typical of granulomatous meningoencephalitis and protozoal diseases. Cerebrospinal fluid white blood cell counts are often normal (sometimes with abnormal distribution of cell types) or mildly elevated. Histologically, mild perivascular cuffing and lymphocytic infiltrates throughout the CNS (i.e., mild, diffuse meningoencephalomyelitis), especially in the cerebellum, characterize CRTS.

It is thought that CRTS may represent an autoimmune-mediated disruption of neurotransmitter metabolism in the CNS, with a decreased conversion of tyrosine to dopamine.

Prognosis for treatment of this disease with immunosuppressive doses of corticosteroids is excellent. Dosages of prednisone may range from 1 to 2 mg/kg body weight, every 12 hr. Once clinical signs have resolved, the corticosteroid

therapy should be gradually discontinued over a 1–3-mo time period. Occasionally, dogs may need to be kept on low doses or alternate day therapy to control the tremors. Some dogs with CRTS benefit from adjunctive oral diazepam therapy (0.2 mg/kg body weight, every 8 hr).

D. Tremorgenic toxins

Numerous toxins are known to either influence cerebellar function resulting in tremors or produce tremors as one of the clinical manifestations of the toxic exposure. Mechanisms of toxin exposure include accidental ingestion, dermal contact, and iatrogenic administration (medications). The mechanisms for the generation of tremors secondary to toxin exposure are not all known. Hexachlorophene, a germicide present in disinfectant solutions, soaps, and shampoos, may produce spongy degeneration of the white matter in the brain, spinal cord, and cerebellum. The ingestion of moldy food containing the mycotoxin penitrem A, produced by *Penicillium* species, may cause clinical signs of ataxia, tremors, and far-off gaze (staring), possibly due to hallucinations. Organophosphates (flea collars, dips), metaldehyde (slug and snail poison), lead, chlorinated hydrocarbons, and bromethalin are common causes of tremors in dogs and cats. Less common are 5-fluorouracil (chemotherapeutic), macadamia nut ingestion, theobromine (chocolate), and strychnine. Many of these toxicants will have other concurrent neurological signs such as seizures and ataxia. Treatment may be specific for the underlying cause or generalized decontamination. Prognosis is variable. More information regarding these toxicities can be found in Chapter 18.

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Chapter 9

MYELOPATHIES: DISORDERS OF THE SPINAL CORD

Curtis W. Dewey

I. Clinical Signs of Spinal Cord Dysfunction

The clinical signs associated with spinal cord dysfunction depend upon the location, size, and rate of development of the lesion. A small lesion on one side of the spinal cord without a great deal of associated cord swelling (e.g., a slowly growing tumor) will likely cause signs predominantly on the side of the lesion. However, a large lesion or a lesion associated with substantial cord swelling (e.g., an acute disk herniation in the thoracolumbar region), will likely result in bilateral signs of dysfunction. In most spinal cord disorders, bilateral deficits will be observed, but the deficits are often more pronounced on the side of the lesion. Proprioceptive and nociceptive information traveling toward the brain, as well as voluntary motor impulses traveling from the brain can be affected with spinal cord disease. With progressive spinal cord disease, proprioception is usually the first deficit observed, followed by deficits in voluntary motor ability, and finally deficits in the ability to perceive painful stimuli (nociception).

The clinical signs listed below for each of the anatomic subdivisions of the spinal cord represent all of the possible abnormalities that may be encountered with lesions in these respective areas. The clinician may, for example, encounter cases of cervical myelopathy in which severe neck pain is the only clinically detectable abnormality. Alternatively, cases may be encountered with more extensive lesions in the same anatomic location in which the patient is tetraplegic with minimal pain perception to the limbs, and having respiratory difficulty. There is a spectrum of possible clinical presentations between these two extreme examples. In this text, the cauda equina is defined as the nerve roots derived from the cord segments L7 and caudally. Damage to the spinal cord segments supplying the cauda equina will produce the same clinical signs of dysfunction as disruption of the respective nerve roots. Disorders of the cauda equina are discussed in more detail in Chapter 10. Nursing care, physical therapy, and complications associated with spinal cord disease are discussed in Chapter 15. Neuronopathies, although technically disorders of the spinal cord, appear clinically as neuropathies; these disorders are discussed in Chapter 12. Tetanus is also technically a spinal cord disorder. Because the sustained muscle rigidity characteristic of tetanus more closely resembles a myopathy than a myelopathy, it is discussed in Chapter 13.

A. C1–C5 spinal cord segments

1. Cervical pain (hyperesthesia).
2. Proprioceptive deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs.

3. Voluntary motor deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs, varying from paresis to plegia. The paresis or plegia (hemiparesis, hemiplegia, tetraparesis, tetraplegia) is upper motor neuron (UMN) in nature, with normal to hyperactive reflex activity in all limbs.
4. Horner's syndrome ipsilateral to the lesion or bilaterally.
5. Respiratory difficulty (severe lesions) involving both chest excursions and diaphragmatic movements.
6. UMN bladder dysfunction (see Chapter 11).
7. Nociceptive (pain perception) deficits are possible in all four limbs.

B. C6–T2 spinal cord segments

1. Cervical pain (hyperesthesia).
2. Proprioceptive deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs.
3. Voluntary motor deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs, varying from paresis to plegia. The paresis or plegia is classically lower motor neuron (LMN) in nature in the thoracic limbs (involvement of the grey matter of C6–T2 or the efferent axonal processes from that grey matter) and UMN in nature in the pelvic limbs. In some instances (e.g., caudal cervical spondylomyelopathy), caudal cervical lesions may result in obvious signs of UMN paraparesis, with subtle or clinically inapparent thoracic limb deficits.
4. Horner's syndrome ipsilateral to the lesion or bilaterally.
5. Decreased or absent cutaneous trunci (panniculus) reflex ipsilateral to the lesion or bilaterally. The deficit is due to impairment of the efferent arm of the reflex arc.
6. Respiratory difficulty with severe lesions. The respiratory pattern often differs from that seen with C1–C5 spinal cord lesions. Since the phrenic nerve arises from spinal cord segments C5–C7, there is usually enough phrenic nerve function to provide diaphragmatic movement, but impulses from the medullary respiratory centers can't effectively traverse the damaged cord segments to stimulate the cell bodies of the intercostal nerves. This is the reason for the "abdominal breathing" pattern seen with severe caudal cervical myelopathies. The thoracic cage moves minimally, if at all, and the exaggerated activity of the diaphragm causes the abdominal contents to move passively.
7. UMN bladder dysfunction (see Chapter 11).
8. Nociceptive deficits are possible in all four limbs.

C. T3–L3 spinal cord segments

1. Thoracolumbar pain (hyperesthesia).
2. Proprioceptive deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs.
3. Voluntary motor deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs. The paresis or plegia (monoparesis, monoplegia, paraparesis,

paraplegia) is UMN in nature, with normal to hyperactive reflex activity in the pelvic limbs.

4. The thoracic limbs are neurologically normal (normal proprioception, normal voluntary motor activity). Schiff-Sherrington posture may be seen in the thoracic limbs (see Chapter 1) and should not be confused with a cervical spinal cord problem. Schiff-Sherrington posture is an anatomic phenomenon, not a prognostic indicator.
5. Horner's syndrome is possible with very cranial lesions (T3 spinal cord level), but less likely in comparison with cervical lesions.
6. Decreased or absent cutaneous trunci (panniculus) reflex, approximately one to four vertebral levels caudal to the spinal cord lesion. The deficit is due to impairment of the afferent arm of the reflex arc.
7. UMN bladder dysfunction (see Chapter 11).
8. Nociceptive deficits are possible in both pelvic limbs.

D. L4–L6 spinal cord segments

1. Lumbar pain (hyperesthesia).
2. Proprioceptive deficits in the pelvic limb are ipsilateral to the lesion or in both pelvic limbs.
3. Voluntary motor deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs. The paresis or plegia (monoparesis, monoplegia, paraparesis, paraplegia) is LMN in nature, with a decreased to absent patellar reflex ipsilateral to the lesion or bilaterally. The withdrawal and gastrocnemius reflexes may be normal or decreased, depending on the extent of damage to the L6 spinal segment (L6 contributes to the sciatic nerve).
4. A decreased or absent panniculus (cutaneous trunci) reflex may or may not be appreciable one to four vertebral levels caudal to the lesion, because the last three or four lumbar spinal nerves do not give off dorsal cutaneous branches.
5. UMN bladder dysfunction (see Chapter 11).
6. Nociceptive deficits are possible in both pelvic limbs.

E. L7–S3 and caudal (coccygeal) spinal cord segments

1. These spinal cord segments give rise to the spinal nerve roots that comprise the cauda equina. Chapter 10 details the clinical signs associated with diseases of the cauda equina.

II. Disorders Affecting the Spinal Cord in Dogs and Cats (Table 9.1)

A. Degenerative

1. Degenerative disk disease^{1–56}
 - a. Degenerative disk disease is a common problem in dogs, but a relatively infrequent clinical disorder in cats. The anatomy associated with both normal and extruded intervertebral disks is illustrated in Figure 9.1. There

Table 9.1: Myelopathies of Dogs and Cats

Degenerative	Anomalous/ developmental	Neoplastic	Nutritional	Inflammatory/ infectious	Ischemic/ vascular	Traumatic	Miscellaneous
Degenerative disk disease	Congenital vertebral malformations	Extradural tumors	Feline hyper- vitaminosis A	Diskospondylitis	Fibrocarti- laginous embolic myelopathy (FCE)	Medical management	Tumoral calcinosis
Caudal cervical spondylomye- lopathy	Stenotic vertebral canal	Intradural/ extramedullary tumors	Methionine deficiency- related spinal myelinopathy	Meningitis/ meningomyelitis	Traumatic feline ischemic myelopathy	Surgical management	Dural ossification Spondylosis deformans
Degenerative myelopathy	Cartilaginous exostoses	Intramedullary tumors					Disseminated idiopathic skeletal hyperostosis (DISH)
Extradural synovial cysts	Meningoceles/ myelomenin- gocles						
Rottweiler leukoencepha- lomyelopathy	Spinal dysraphism						
Leukodystrophies	Hydromyelia/ syringomyelia						
Hereditary ataxia							
Labrador retriever axonopathy	Pilonidal sinus Spinal arachnoid cysts						
Lysosomal storage disease							

are two basic types of disk degeneration, referred to as chondroid and fibroid degeneration. These two types of degeneration typically cause two distinct types of disk disease. In chondroid degeneration, the normally gelatinous nucleus pulposus loses water-binding capacity, undergoes degradation of the glycosaminoglycan components, and often becomes calcified. The dorsal annulus often weakens, and the abnormal nucleus pulposus contents extrude through the weakened annulus into the vertebral canal. This type of disk disease is called Hansen Type I, or simply Type I, disk extrusion. The severity of spinal cord damage caused by Type I disk extrusion is believed to be related to the rate of extrusion (force of impact or concussion), duration of compression, and amount of disk material extruded. Fibroid degeneration involves a progressive thickening of the dorsal annulus fibrosus, which protrudes dorsally into the vertebral canal. This type of disk disease is called Hansen Type II (Type II) disk protrusion.

- b. Clinical features of both types of disk disease are listed below:
- (1) Hansen Type I extrusions typically occur in small-breed dogs, particularly the chondrodystrophic breeds (Dachshunds, Beagles, Bassett hounds, etc.). Hansen Type II disk protrusions typically occur in non-chondrodystrophic, larger-breed dogs. Either type of disk disease can occur in any breed of dog, however. In a recent report of disk disease in large (more than 15 kg) nonchondrodystrophic dogs, 92% of the cases were found to have Type I disk extrusions.
 - (2) Hansen Type I extrusions typically occur in dogs three years old or older, but may occur in dogs younger than this. In one study, the mean age of cats with thoracolumbar Type I disk extrusions was 9.8 yr; no breed or sex predilection was found in that study. Hansen Type II protrusions typically occur in dogs five years of age and older.
 - (3) Hansen Type I disk extrusions usually cause rapidly developing clinical signs (minutes-days), whereas Hansen Type II disk protrusions typically cause chronically developing clinical signs (weeks-months).
 - (4) Both types of disk disease may affect cervical, caudal thoracic, and lumbar disks. Type I cervical disk disease usually affects cranial cervical disks (C2–C3 most commonly), and typically causes severe neck pain, usually with inapparent or mild neurologic deficits. The patient often adopts a “nose-down” posture with an arched back (Fig. 9.2). When turning, these dogs tend to move the head and the neck as one unit, rather than bending at the neck. Fasciculations of the neck musculature can often be appreciated, especially upon palpation of the neck. Occasionally, these dogs will scream in apparent pain and fall over. This may be mistaken for seizure activity by the owner. Lameness of one thoracic limb, referred to as “root signature” is exhibited sometimes, and is thought to be caused by irritation of cervical nerve roots

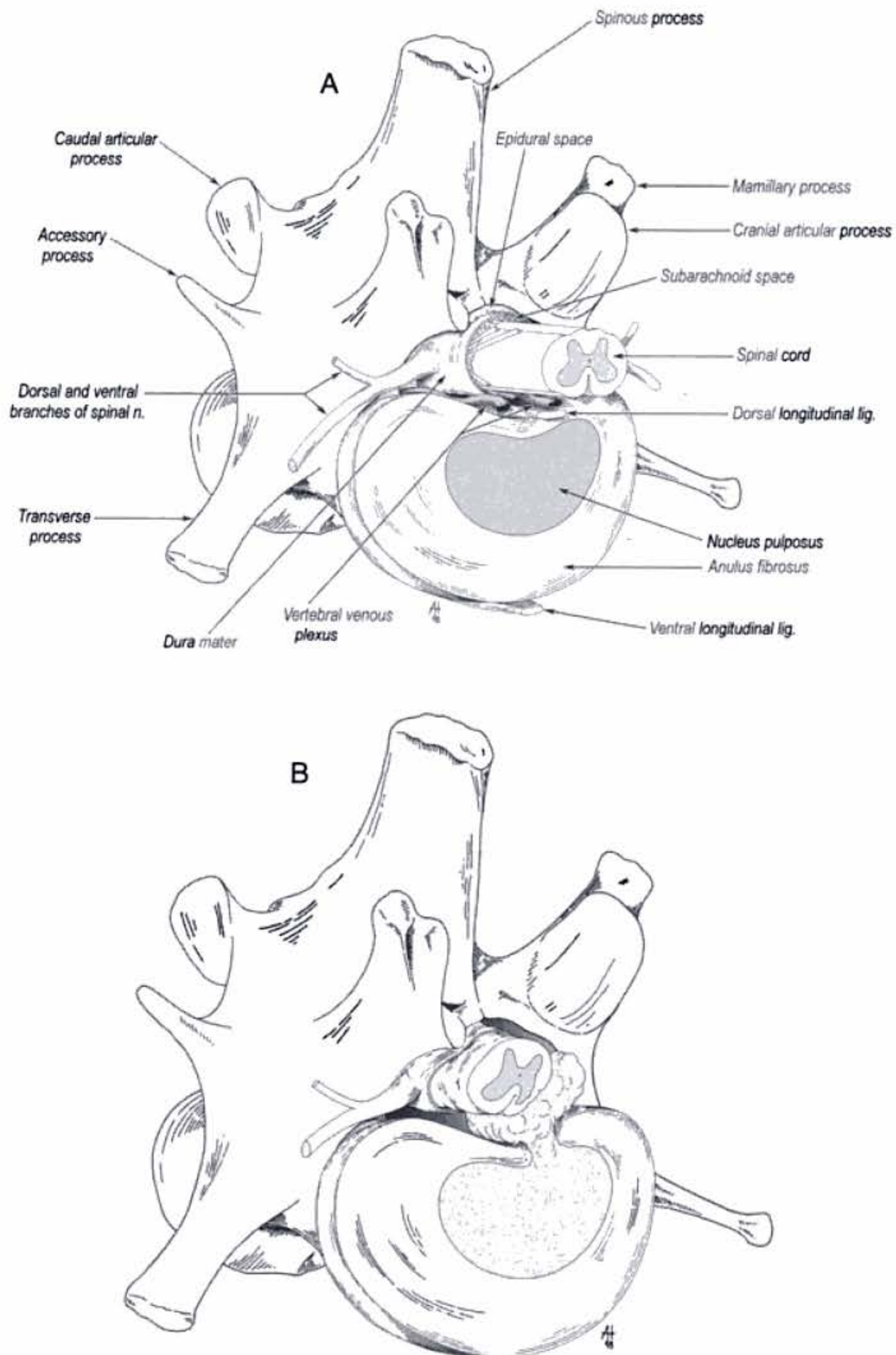


Fig. 9.1. Anatomic structures associated with a normal (A) and extruded (B) thoracolumbar disk (Illustration by Anton Hoffman).

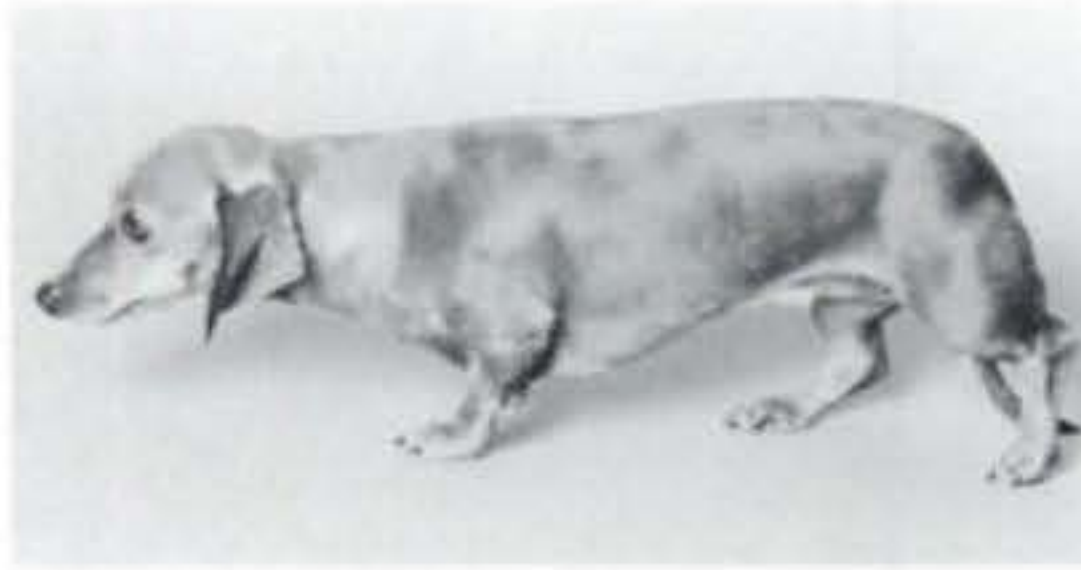


Fig. 9.2. Typical posture of a dog with a Type I cervical disk extrusion (Courtesy of Dr. Joan Coates).

by laterally extruded disk material. Pelvic limb root signature is less commonly encountered. In many cases of root signature, the abnormal limb will be held in a flexed position and caudal extension of that limb elicits a painful response (presumably due to stretching of irritated nerve roots).

Type II cervical disk disease may result in clinically appreciable neck pain, but rarely to the degree encountered in Type I cervical disk disease. Type II cervical disk disease usually causes slowly progressive paresis. This can occur as an isolated process, or as a component of caudal cervical spondylomyelopathy (discussed later in this chapter).

- (5) Disk disease in the thoracolumbar region is more frequently encountered than cervical disk disease. Disk problems cranial to the T10–T11 disk space are uncommon, probably due to the stabilizing influence of the intercapital ligament. This ligament passes over the dorsal annulus from rib head to rib head in all but the first pair and last two pairs of ribs. Type I disk extrusions usually occur between vertebral levels T11 and L3. The T12–T13 and T13–L1 disks are the most common sites for Type I disk extrusions to occur in small-breed dogs. In larger dogs, the L1–L2 and L2–L3 disk spaces are the most common sites for Type I extrusions. The L4–L5 intervertebral disk space appears to be the most common site for thoracolumbar disk extrusion in cats.

While patients with signs of back pain with minimal to no neurologic deficits are occasionally encountered, Type I thoracolumbar disk extrusions more typically result in acute paraparesis or paraplegia (Fig. 9.3). This may be due to the limited epidural space in the thoracolumbar vertebral canal, as compared to the cervical region. These patients often exhibit back pain in the general area of the disk extrusion. Type II thoracolumbar disk protrusions typically cause progressive signs of paraparesis, often with some degree of back pain. Protrusion of the L7–S1 disk is often a component of degenerative lumbosacral stenosis and will be discussed separately in Chapter 10.



Fig. 9.3. Typical posture of a dog with a severe Type I thoracolumbar disk extrusion.

- c. Diagnosis of disk disease is based upon signalment, history, clinical signs, and results of diagnostic tests such as cerebrospinal fluid (CSF) analysis, and imaging of the spine. Traditional spinal imaging for pets with suspected disk disease consists of plain radiographs followed by myelography, both performed under general anesthesia (Fig. 9.4). Computed tomography (CT) and magnetic resonance imaging (MRI) have been found to be useful imaging modalities in the diagnosis of intervertebral disk disease (Fig. 9.5). In some instances (e.g., lateralized Type I extrusions), CT or MRI may be preferred (Fig. 9.6).

The decision of what diagnostic tests, if any, to perform for an individual case usually depends on the expected treatment protocol for that patient. For example, a young Dachshund with acute onset of neck pain and no neurologic deficits is likely to have a Type I cervical disk extrusion, and will likely respond to cage confinement with or without anti-inflammatory drugs. It would be illogical to anesthetize this patient and perform myelography to confirm the most likely diagnosis if surgical therapy is not the treatment protocol of choice at that time.

The typical myelographic (or CT/MR) finding in disk extrusion/protrusion is extradural spinal cord compression centered over a disk space. Occasionally, a Type I disk extrusion will be lateral enough that myelographic results are normal. In such lateralized extrusions, hyperesthesia with or without unilateral limb lameness (ipsilateral to the extrusion) are more likely clinical signs of dysfunction than overt proprioceptive or voluntary motor deficits.

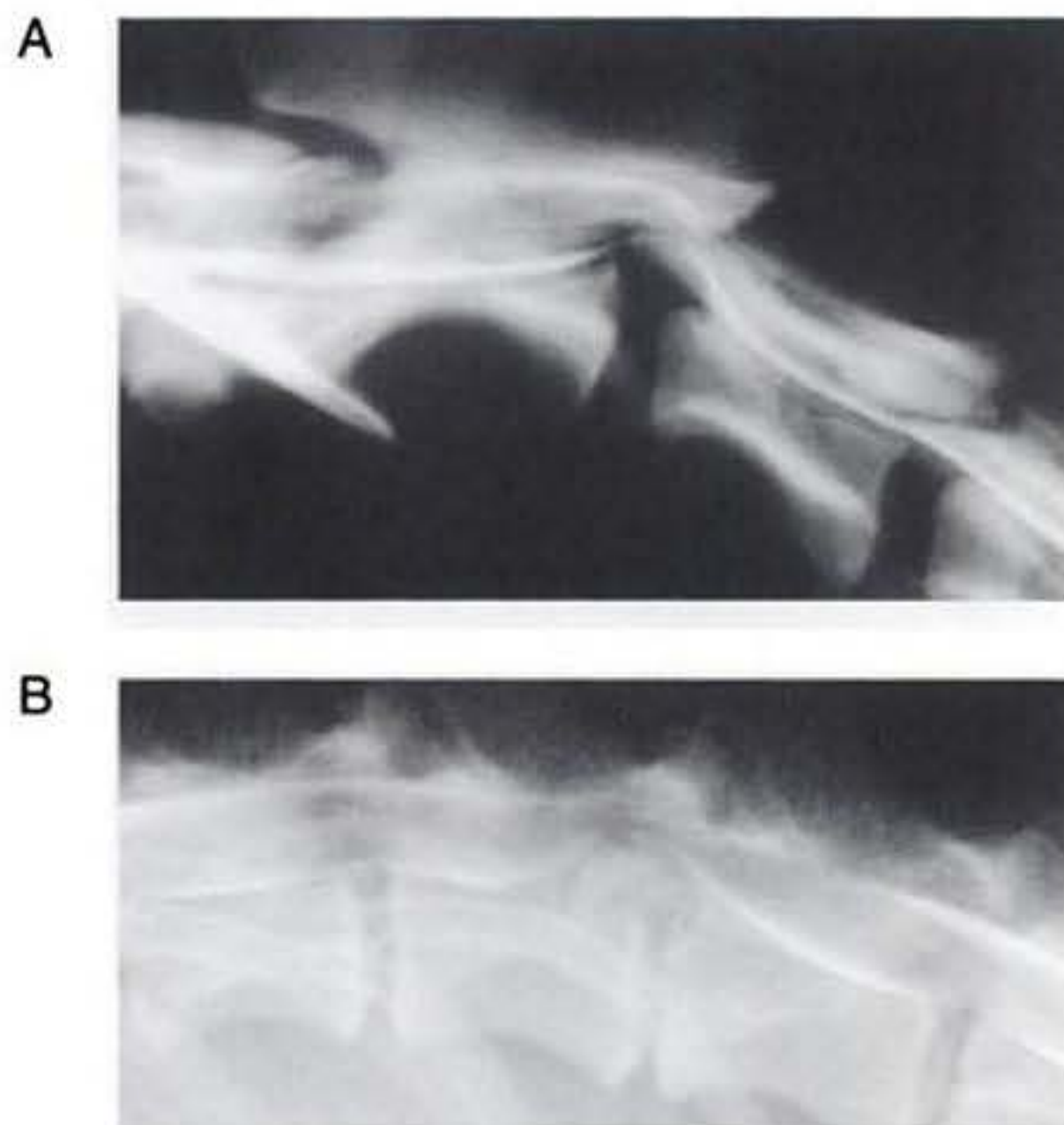


Fig. 9.4. Lateral myelographic views of an extruded cervical disk (A) and an extruded thoracolumbar disk (B).

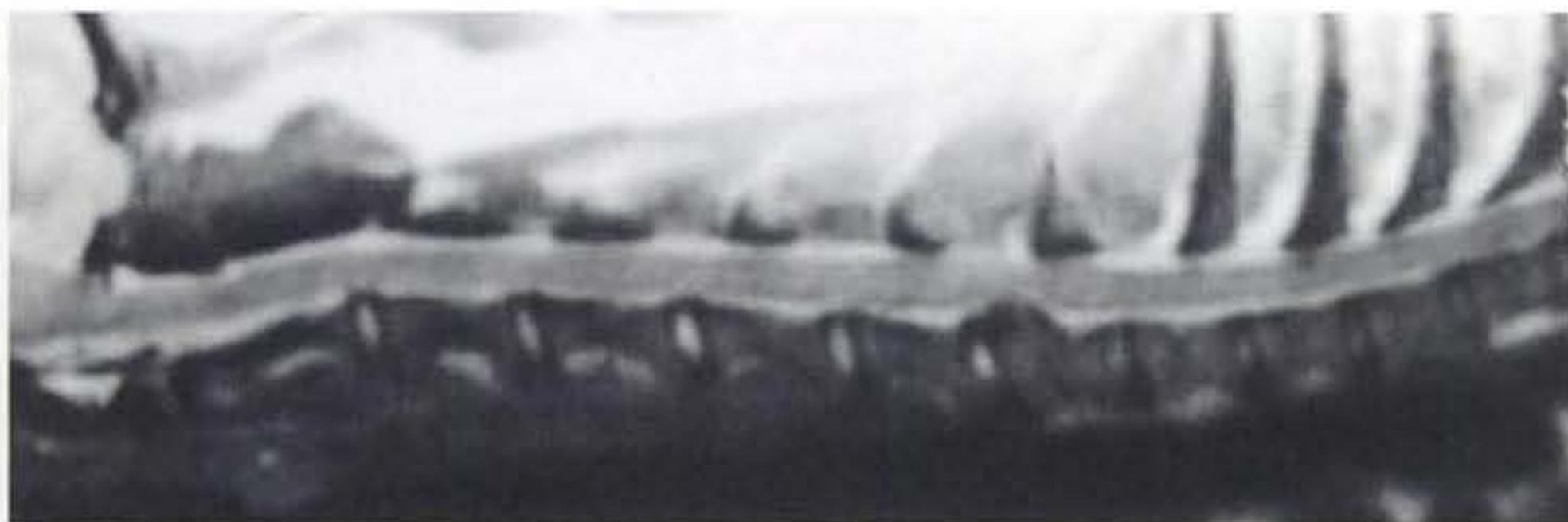


Fig. 9.5. Sagittal MR image (T2-weighted) of a disk extrusion at the C6–C7 level.

- d. Treatment of acute and chronic disk disease is a subject of considerable debate, but there are a number of established guidelines. The guidelines center around whether or not to include surgical intervention as part of the patient's therapy. There are positives and negatives associated with surgical and nonsurgical management of disk disease patients, and the clients need to be informed of the benefits and risks associated with either approach.

Patients with suspected Type I cervical or thoracolumbar disk extrusions are often successfully treated nonsurgically initially if they exhibit

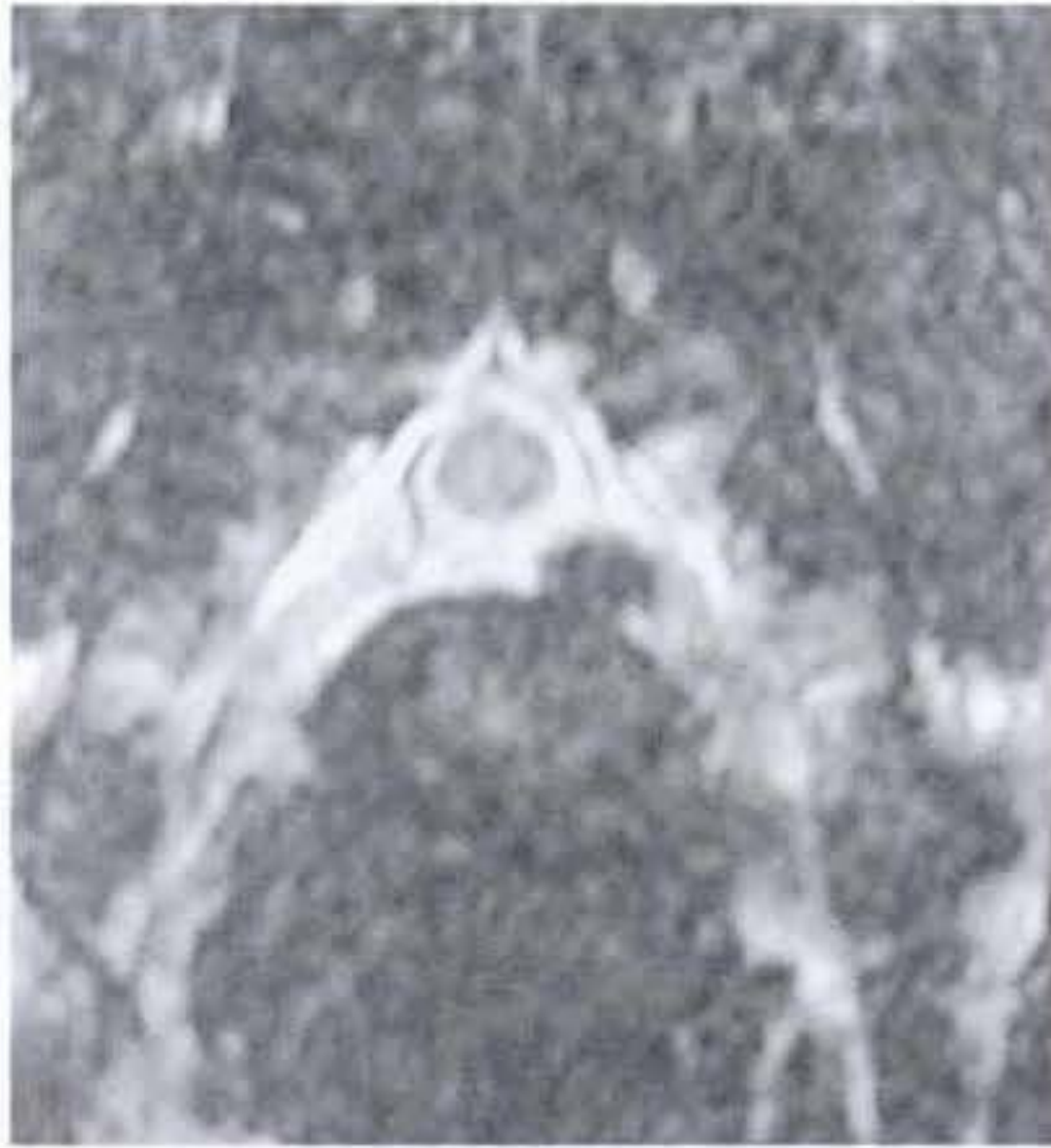


Fig. 9.6. Transaxial MR image (T2-weighted) demonstrating lateralized disk material.

mild to no neurologic deficits (i.e., mainly neck or back pain) and have not had repeated episodes of pain. Medical management consists of strict cage confinement for 3–4 wk, with or without anti-inflammatory medication. The cage or crate should be of such size that the patient can change positions, but can not walk around or jump. Activity should be restricted to short walks to urinate/defecate, at which times the owner can assess the progress of the patient. If the patient fails to improve or worsens at any time during the confinement period, surgical options should be pursued. If necessary, it is acceptable to administer an anti-inflammatory dose of prednisone in a decreasing regimen, such as the following:

- (1) 0.5 mg/kg, PO, every 12 hr for 5–7 days.
- (2) 0.5 mg/kg, PO, every 12 hr, every other day, (i.e., skip a day) for the following 5–7 days.
- (3) 0.5 mg/kg, PO, every 48 hr, for the final 5–7 days.

It is *unacceptable* to administer anti-inflammatory drugs to a patient exhibiting signs of an extruded disk, without concurrently confining that patient. The anti-inflammatory drugs alleviate the patient's pain, and most dogs will subsequently become more active. Increased activity is thought to cause more pressure to be placed on the abnormal disk by the adjacent vertebrae; subsequently, more disk material is extruded into the vertebral canal, and clinical signs acutely worsen. It is also *unacceptable* to concurrently administer steroidal and nonsteroidal anti-inflammatory drugs to

disk disease patients, as this increases the chances of severe gastrointestinal complications.

Many dogs will respond favorably to confinement (nonsurgical) management. Enforced rest is thought to minimize further disk extrusion into the vertebral canal, while allowing tears in the annulus fibrosus to heal (preventing further disk extrusion). The inflammatory reaction caused by the extruded disk material is thought to subside during this enforced resting period. If confinement therapy is successful, the patient should be gradually allowed to return to a normal level of activity over a period of 4–6 wk. The owners need to be informed that the patient may acutely worsen during confinement and, especially with thoracolumbar disk disease, may become a surgical emergency.

Type II disk disease that is not associated with cervical spondylomyelopathy or degenerative lumbosacral stenosis is typically managed medically with restricted activity and anti-inflammatory drugs. The injection of proteolytic enzymes (e.g., chymopapain) into Type II disks to dissolve the nucleus pulposus and cause flattening of the protruded annulus has been recently evaluated and may hold some promise as a treatment for this disease. When surgical intervention is indicated for a disk disease patient, spinal radiographs, CSF analysis, and myelography should ideally all be performed on the anesthetized patient prior to surgery. In this text, surgical intervention for disk disease specifically refers to those procedures that allow for decompression of the spinal cord and removal of disk material from the vertebral canal (e.g., ventral slot, hemilaminectomy, dorsal laminectomy). Disk fenestration is considered to be an optional, ancillary surgical procedure. Fenestration involves removing a segment of annulus fibrosus, so that future extrusions will likely occur through that opening, rather than into the vertebral canal. The fenestration is performed in the ventral aspect of the disk in the cervical region, and the lateral aspect of the disk in the thoracolumbar region. Disk fenestration is considered to be a prophylactic measure. The efficacy of fenestration remains to be definitively proven.

Surgical intervention is the preferred treatment modality for the following scenarios:

- (1) Suspected Type I cervical or thoracolumbar disk disease patients with minimal to no neurologic deficits, but repeated episodes of pain, or pain that is not responding to proper confinement therapy.
- (2) Suspected Type I cervical disk disease patients with moderate to severe neurologic deficits (tetraparesis, tetraplegia). An acutely tetraplegic patient should be handled as a surgical emergency.
- (3) Suspected Type I thoracolumbar disk disease patients that are nonambulatory. This includes patients that are nonambulatory paraparetic (voluntary motor ability to hindlimbs present, but can't walk unassisted)

and those that are paraplegic (no voluntary motor ability to pelvic limbs). These patients are to be considered as surgical emergencies, as many will continue to deteriorate to the point of losing pain perception to the pelvic limbs, if surgical intervention is not pursued quickly.

- (4) Suspected Type I cervical or thoracolumbar disk disease patients exhibiting obvious deterioration in neurologic status, whether or not the patient is still ambulatory. The surgical procedure of choice for cervical disk extrusions is usually a ventral slot procedure (Fig. 9.7),

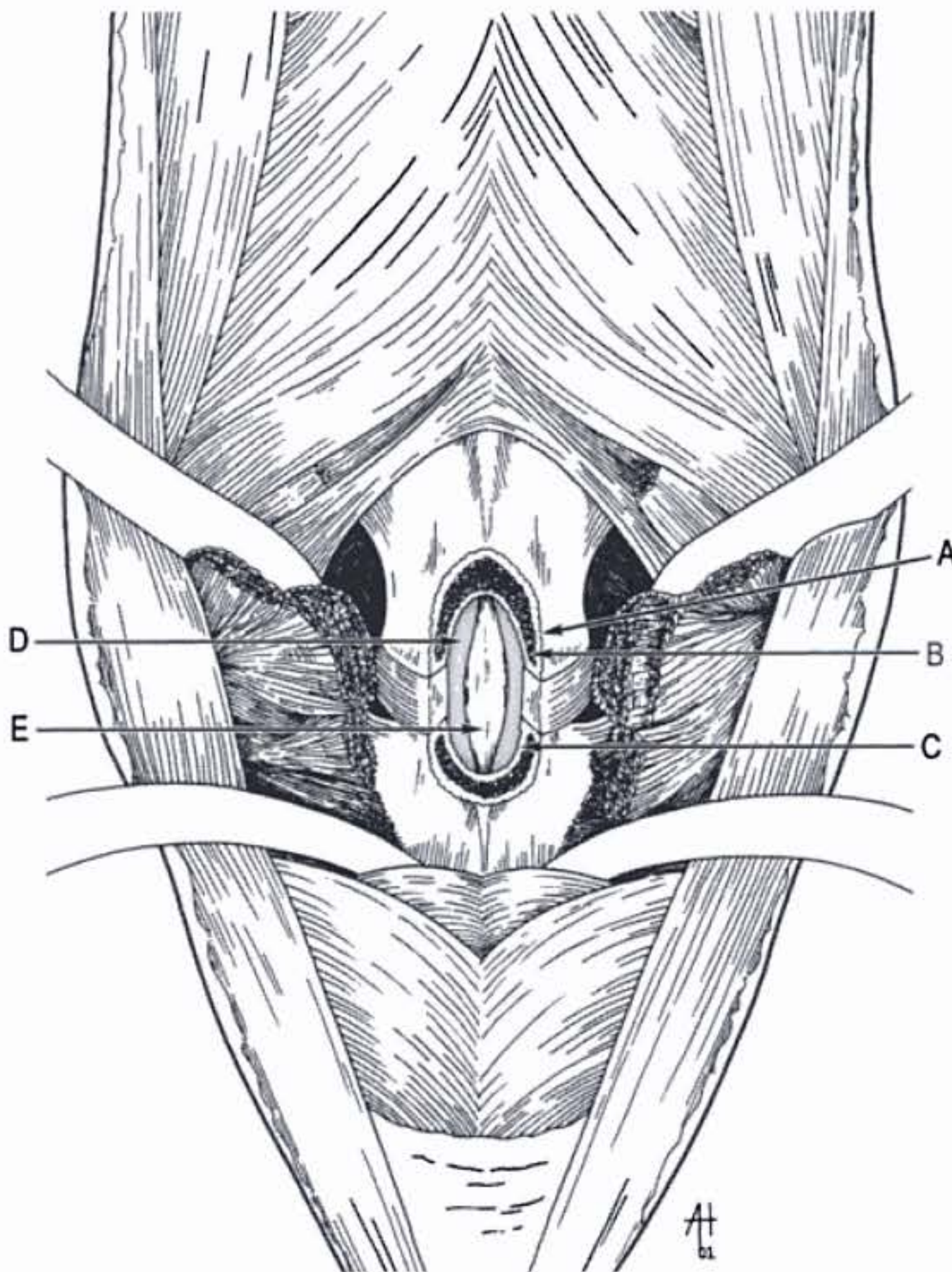


Fig. 9.7. Schematic illustration of a ventral slot procedure (Illustration by Anton Hoffman, from: Coates JR, Hoffman AG, Dewey CW, Surgical approaches to the spine, in Slatter D (ed), *Textbook of Small Animal Surgery*, 3d ed. Philadelphia, WB Saunders Co, 2002. Reprinted with permission). A, outer cortical bone; B, cancellous bone; C, inner cortical bone; D, paired venous sinuses; E, dorsal longitudinal ligament.

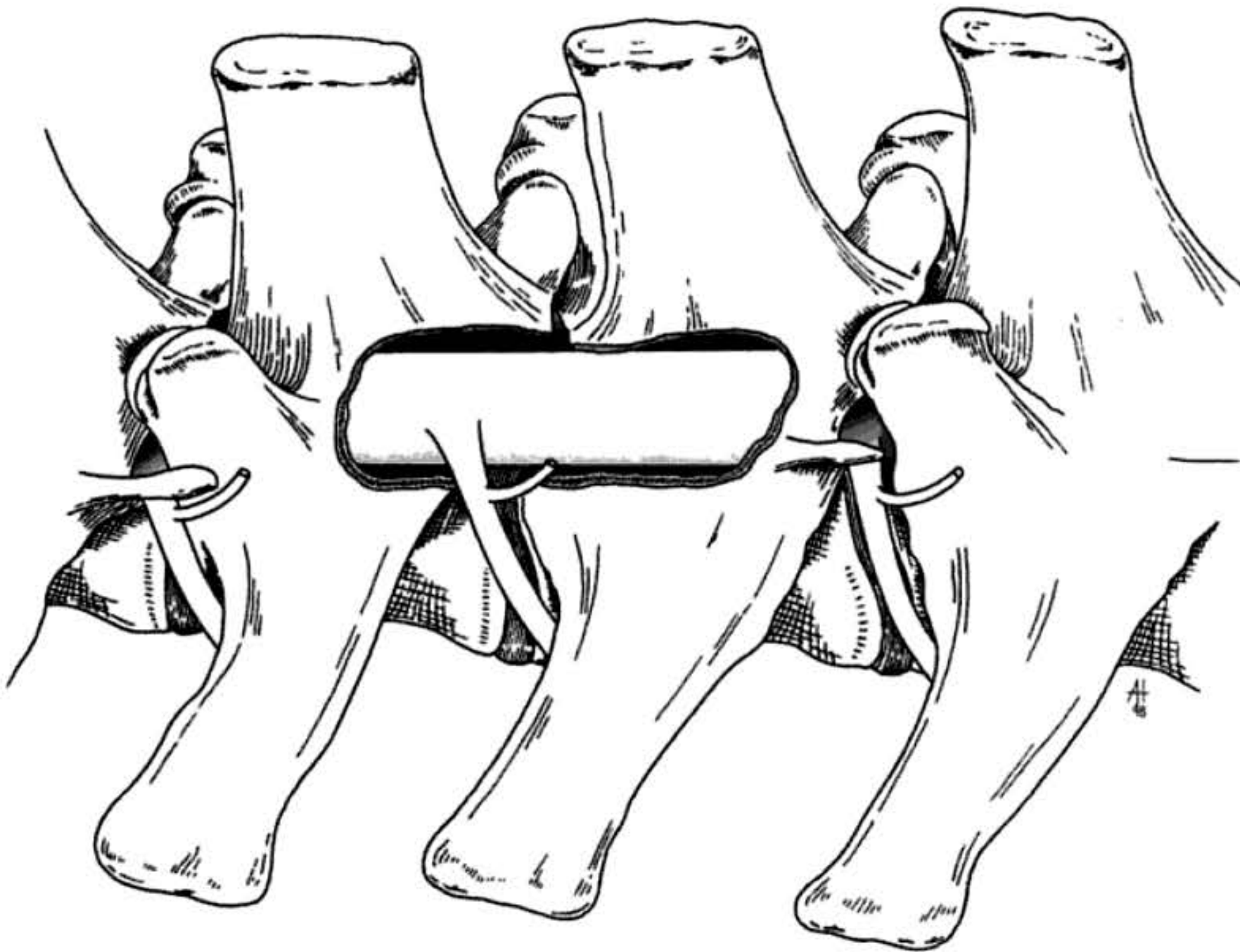


Fig. 9.8. Schematic illustration of a hemilaminectomy in the lumbar spinal region (Illustration by Anton Hoffman).

and for thoracolumbar disk extrusions, either a hemilaminectomy (Fig. 9.8) or dorsal laminectomy (Fig. 9.9). Occasionally, a dorsal laminectomy is indicated for cervical disk extrusions (Fig. 9.10), in which there is dorsal or lateral accumulation of disk material and/or extensive spinal cord swelling (Fig. 9.11). Fenestration of disks as a prophylactic maneuver is commonly performed in both the cervical and thoracolumbar regions, usually concurrently with a ventral slot or hemilaminectomy, respectively.

Surgery is sometimes required in cases of Type II disk disease, and the surgical procedures employed are generally the same as those used for Type I disk disease. Specific surgical options available for caudal cervical spondylomyelopathy and disk-related cauda equina syndrome are discussed elsewhere in this text. Despite lack of evidence of efficacy, aggressive glucocorticoid therapy is often recommended for Type I disk extrusion patients with rapid development of moderate to severe

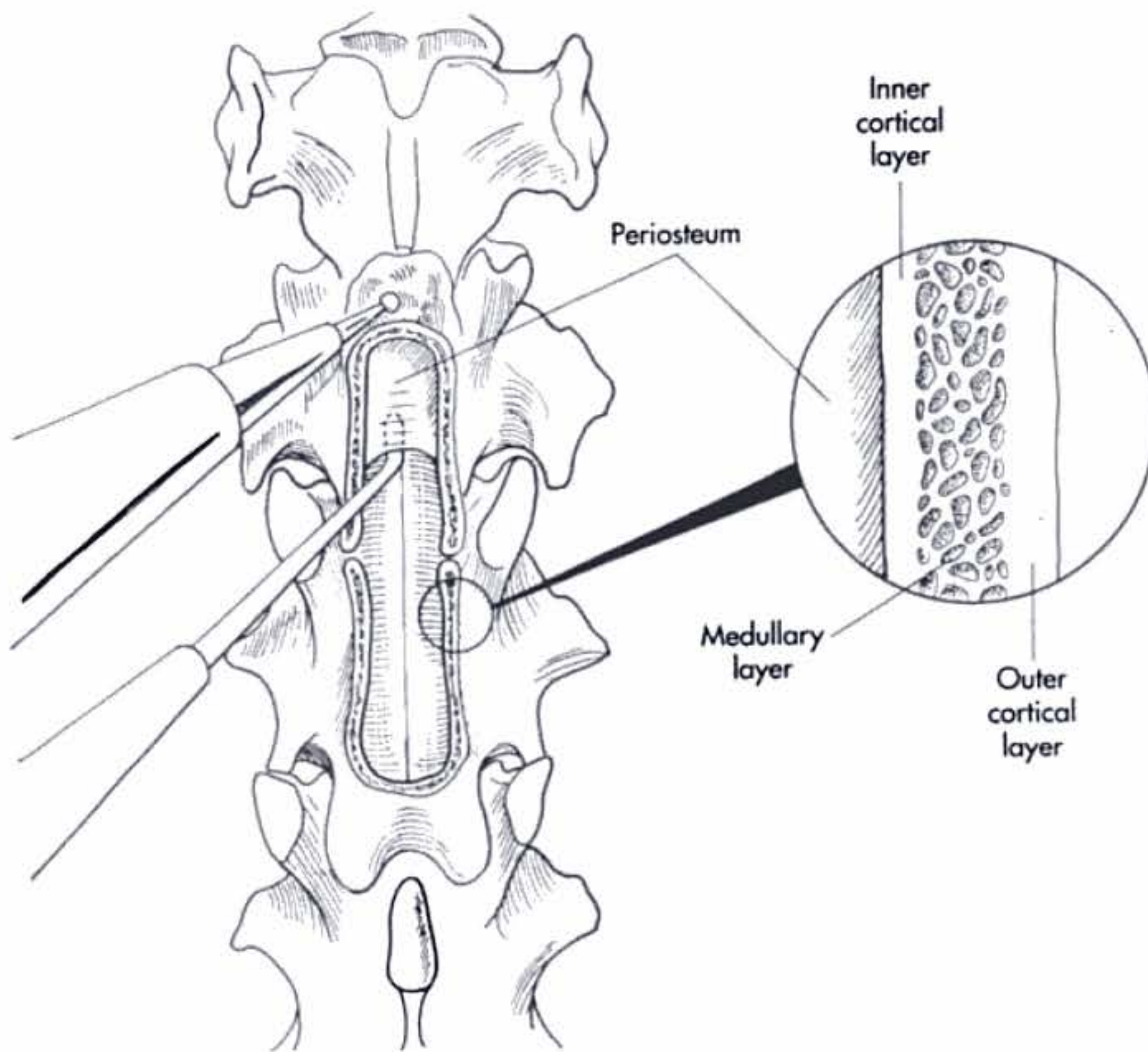


Fig. 9.9. Schematic illustration of a dorsal laminectomy in the thoracolumbar region of the spine (From Fossum TW, et al., *Small Animal Surgery*, 2d ed., 2002. Reprinted with permission).

neurologic dysfunction (e.g., paralyzed Dachshund). Although glucocorticoid administration is often associated with minimal clinical consequences, complications ranging in severity from vomiting/diarrhea to fatal colonic perforation have been reported. The only glucocorticoid treatment that has been demonstrated to be of some potential benefit in spinal trauma is the “high-dose” methylprednisolone sodium succinate (MPSS) protocol. This protocol is discussed in Chapter 5 and in the section on spinal trauma (later this chapter). Recently, the therapeutic efficacy of high-dose MPSS in human spinal trauma has been questioned. In another recent report, high-dose MPSS therapy had no beneficial effect on outcome in surgically treated Dachshunds with Type I disk extrusions; MPSS therapy was associated with a significantly increased level of gastrointestinal complications in that study.

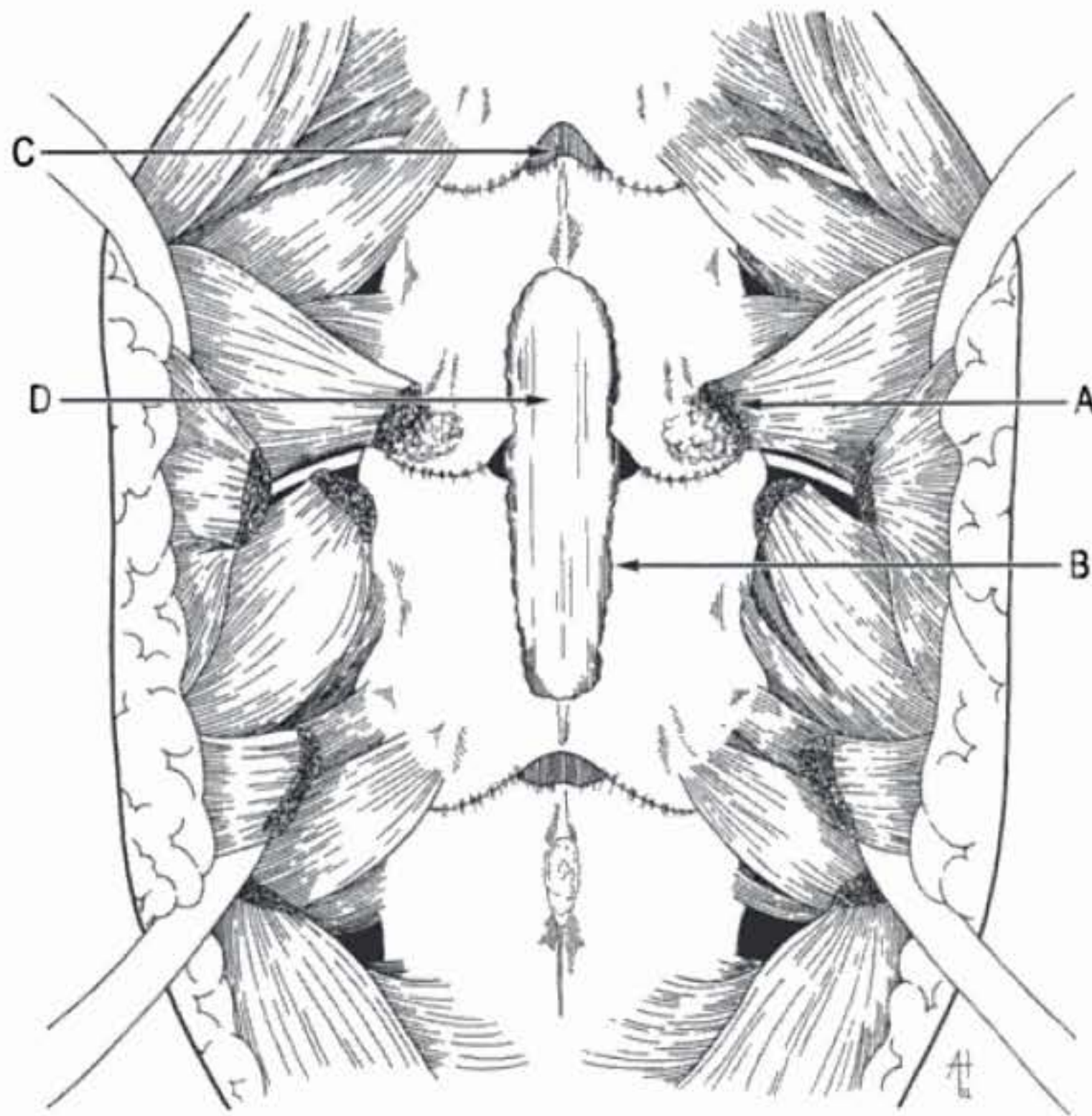


Fig. 9.10. Schematic illustration of a dorsal laminectomy in the cervical region of the spine (Illustration by Anton Hoffman, from: Coates JR, Hoffman AG, Dewey CW, Surgical approaches to the spine, in Slatter D (ed), *Textbook of Small Animal Surgery*, 3d ed. Philadelphia, WB Saunders Co, 2002. Reprinted with permission). A, multifidus musculature; B, laminectomy margin; C, yellow ligament; D, spinal cord.

The prognosis for functional recovery in Type I cervical and thoracolumbar disk disease patients is generally good to excellent. Functional recovery for surgically treated patients with Type I thoracolumbar disk extrusions and intact pain perception (nociception) to the pelvic limbs is expected in 80–95% of cases. The average time to ambulatory status following surgery in these patients is approximately 2 wk. There is no difference in outcome between dogs with UMN and LMN pelvic limb dysfunction. The prognosis appears to be similarly favorable for cats with intervertebral disk extrusions treated surgically.

In a recent study of dogs with Type I thoracolumbar disk extrusion and intact deep pain perception (DPP), an inverse relationship was found between the time from nonambulatory status to surgical intervention and the time from surgical intervention to regaining



Fig. 9.11. Ventrrodorsal myelographic image showing a lateralized disk extrusion in the region of the C4–C5 intervertebral disk space.

ambulatory function. These results do not diminish the need for expediency in operating patients without voluntary motor function. However, they suggest that patients with more rapid loss of motor function sustain more severe spinal cord injury than those dogs with more progressive loss of motor function. The former animals likely sustain more severe concussive (force of impact) spinal cord injury at the time of disk extrusion, which may be more damaging than progressive compression.

The loss of clinically detectable DPP in the pelvic limbs occurs with some frequency in Type I thoracolumbar disk disease, and is associated with a guarded to poor prognosis. In this subset of patients, the amount of time elapsed from the loss of DPP to surgical decompression has been inversely associated with prognosis. Unfortunately, an accurate estimate of when deep pain perception was lost is not always attainable in clinical practice. Most reports suggest a functional recov-

ery rate in the vicinity of 50% (between 20% and 70%) for paraplegic dogs that have lost DPP to the pelvic limbs. Peracute (less than 1 hr) loss of voluntary motor function has been associated with a statistically significantly worse prognosis for functional recovery, compared with acute (1–24 hr) or gradual (more than 24 hr) loss of voluntary motor function in these dogs. Similar to the situation in dogs with intact DPP, acute concussive spinal cord injury in dogs without DPP seems to be more related to eventual outcome than duration of spinal cord compression. There is a tendency for better functional results when dogs with absent DPP are operated on within 12 hr of losing DPP. The contention that the absence of DPP for more than 48 hr precludes a chance for functional recovery after surgery is probably inaccurate. The development of myelomalacia (liquefaction of the spinal cord parenchyma) is a concern with dogs that have lost pain perception, and can usually only be ruled in or out at surgery. Myelomalacia will be discussed in more detail under Spinal Trauma (this chapter).

Cervical Type I disk extrusions severe enough to cause respiratory compromise are rare, and are often associated with a poor prognosis. However, with appropriate respiratory support (i.e., ventilator therapy) following surgery, the majority of these cases are likely to recover ambulatory function within 2–3 mo.

Recurrence of clinical signs of disk extrusion for surgically treated Type I disk disease patients is reported to be between 10% and 25%, but the vast majority of these recurrences do not require repeat surgical intervention. In one report, the reoperative rate for dogs with thoracolumbar Type I disk extrusions was found to be 6.4%. Most (83%) recurrent disk extrusions occurred more than one month from the time of the initial surgery, and the majority of these (88%) were from a separate disk site. All recurrent disk extrusions occurring less than one month after the initial surgery were from the initial disk extrusion site. Dogs were found to be just as likely to achieve functional recovery following repeat surgery as they were after the initial surgery. Dachshunds are thought to be at highest risk for reoperative disk extrusions, compared with other breeds (almost 10%).

Patients with Type II disk disease are often controlled adequately for long periods of time with medical therapy. The prognosis for surgical treatment of Type II disk disease is generally guarded, as compared with Type I disease, especially for lesions in the thoracolumbar spinal cord. Substantial, sometimes permanent, neurologic deterioration after surgery is more likely in these patients. The reason(s) for this phenomenon is(are) unknown, but may be due to such factors as reperfusion injury and lack of spinal cord functional reserve capacity (due to chronic compression).

2. Caudal cervical spondylomyelopathy (“wobblers syndrome”) ^{1,11,57–75}

- a. This syndrome refers to a combination of vertebral malformation and malarticulation affecting the caudal cervical vertebrae and associated ligamentous structures, usually in middle-aged to older, large-breed dogs. The chronic instability from the malformation/malarticulation is thought to lead to hypertrophy of soft tissue supportive structures over time, with subsequent impingement of the spinal cord. A congenital bony stenosis of cervical vertebrae occurring in young (less than 2 yr) dogs (Great Danes, Doberman Pinschers, Bassett hounds) can also cause signs of cervical myelopathy. This latter disease process is relatively uncommon, and the following information refers to the syndrome usually seen in middle-aged to older dogs. This syndrome principally affects adult Doberman Pinschers, but other large-breed dogs are occasionally affected. The C5–C6 and C6–C7 disk spaces are most commonly affected. Caudal cervical spondylomyelopathy (CCSM) has also been reported in small-breed dogs, most notably following ventral slot procedures. Instability in these dogs may have been due to excessive ventral slot size, with subsequent intervertebral instability.
- b. Clinical signs are consistent with a caudal cervical myelopathy, with the pelvic limbs usually more obviously affected than the thoracic limbs. If ambulatory, these patients typically exhibit a stiff, choppy, shuffling thoracic limb gait and an ataxic, wide-based, pelvic limb gait. Proprioceptive deficits are usually more appreciable in the pelvic limbs than in the thoracic limbs, and it may be difficult to distinguish these patients as having a C6–T2, rather than a T3–L3 myelopathy. These dogs may display neck pain, but it is often subtle. Low head carriage (flexed neck position) and resistance to lateral movement and extension of the neck may be appreciated. Onset of clinical signs is typically slowly progressive over weeks to months, but is occasionally acute and associated with some minor traumatic event.
- c. Diagnosis typically depends on myelography, with stress (flexion, extension, linear traction) views (Fig. 9.12). These different views are necessary (especially linear traction) to adequately define the specific abnormalities and to guide surgical decision making, if that route is chosen.

Recently, both CT and MR imaging have been demonstrated to be useful imaging modalities for CCSM. The author prefers MR imaging, including linear traction views, for CCSM cases. One or more of the following abnormalities at one or more disk spaces may be observed:

- (1) Ventral compression, from a malaligned vertebral body, protruded dorsal annulus, and/or hypertrophied dorsal longitudinal ligament.
- (2) Dorsal compression, from hypertrophied ligamentum flavum.
- (3) Lateral compression, from hypertrophied articular facet joint capsules.

Linear traction views often relieve these compressive lesions, whereas extension views often exacerbate them. Extension views should be performed cautiously. A change in the character of the lesion(s) with different

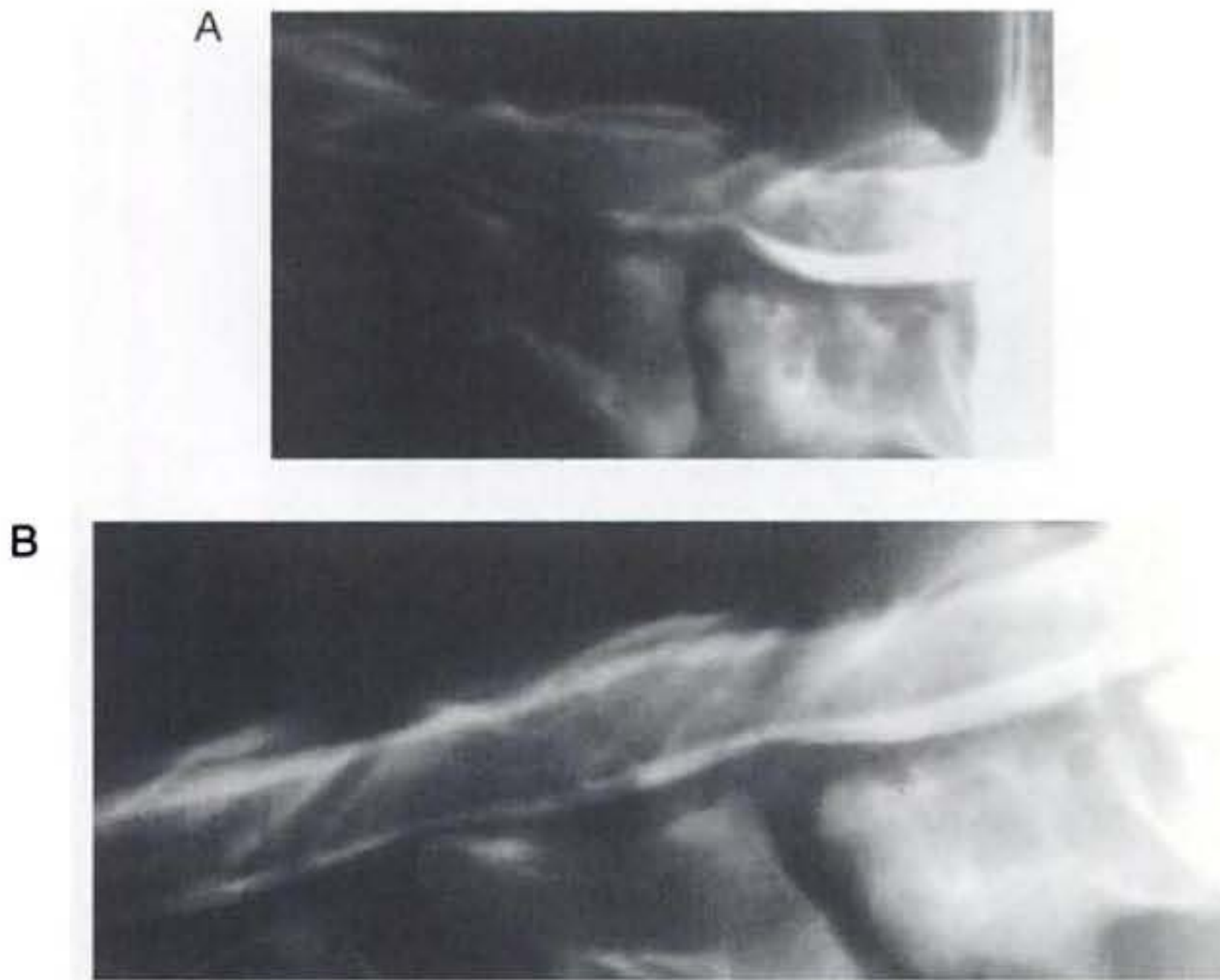


Fig. 9.12. Lateral myelographic images of a CCSM lesion at the C6–C7 intervertebral disk space, before (A) and after (B) application of linear traction.

views suggests that it is a dynamic, rather than a static (e.g., isolated Type II disk protrusion) disorder.

- d. Medical treatment can be attempted in this disorder, consisting of cage confinement (3–4 wk), anti-inflammatory medication (e.g., prednisone), and potentially the use of a neck brace. As with other disk-associated problems, the patient should be gradually returned to normal activity over 4–6 wk, if the initial cage confinement therapy is successful. Surgical therapy is often pursued, as CCSM is typically a progressive syndrome, and medical therapy is often ineffective or effective only transiently. There have been numerous surgical procedures advocated for this syndrome and they fall into two major categories:
 - (1) Ventral approach—this usually involves a ventral slot procedure at the affected space, combined with distraction-stabilization often with cancellous bone grafting at that space. Commonly employed distraction-stabilization procedures include pin or screw placement into vertebral bodies with a polymethylmethacrylate (PMMA) bridge, and PMMA “plug” insertion into the distracted ventral slot. The author prefers a combination procedure utilizing both techniques (Fig. 9.13).
 - (2) Dorsal approach—this involves a dorsal laminectomy for decompression, with or without articular facet screws or pins to help stabilize the joint

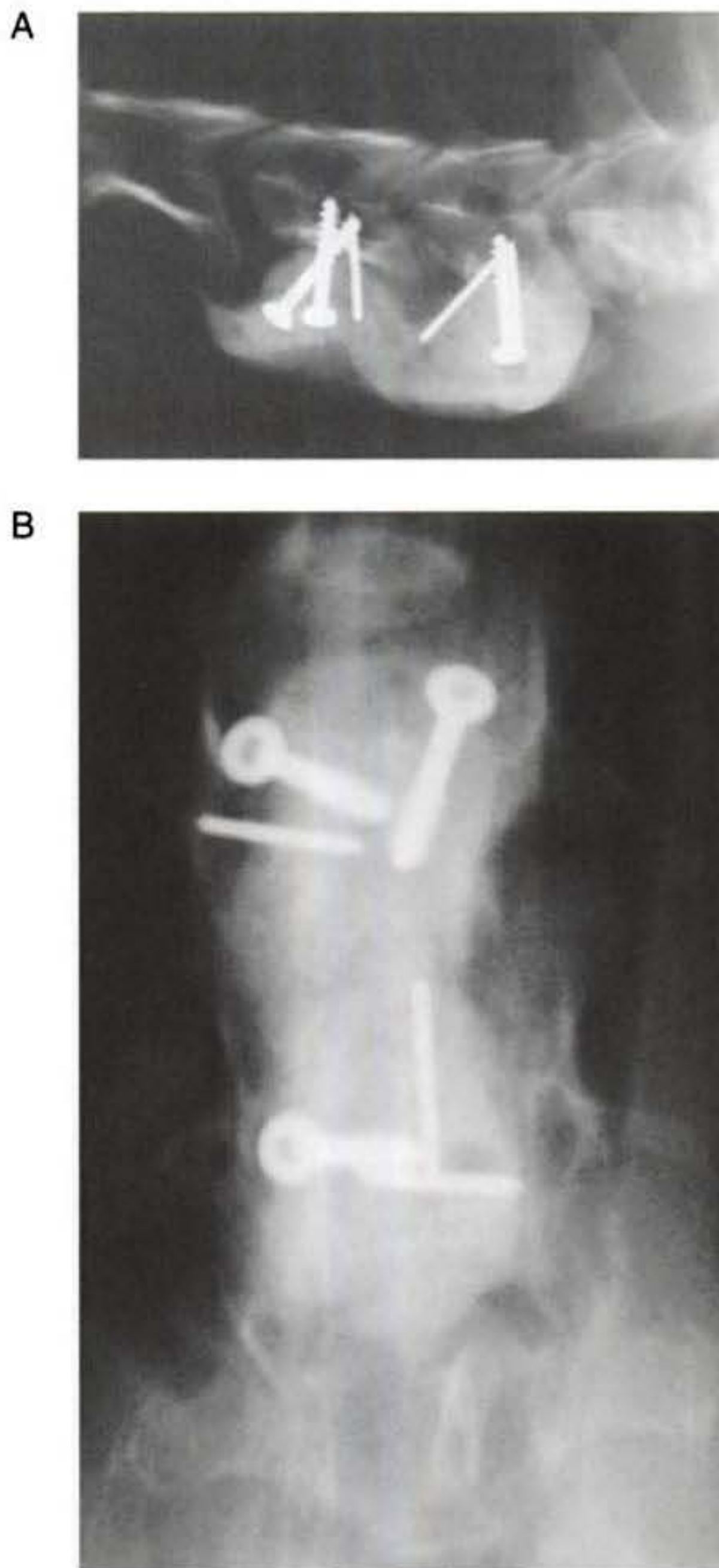


Fig. 9.13. Lateral (A) and ventrodorsal (B) postoperative radiographs of a CCSM lesion surgically addressed via a distraction-stabilization procedure.

space. The dorsal approach may be preferable when multiple disk spaces are affected, or the compression is primarily dorsal or lateral.

Surgical stabilization of one disk space may lead to abnormal biomechanical stresses on spaces cranial and caudal to those spaces. This is

thought to lead to secondary lesions at these latter spaces over time and is referred to as the “domino effect.”

The prognosis for dogs with caudal cervical spondylomyelopathy is generally good, but it is somewhat unpredictable, compared to Type I disk extrusions. Also, many dogs require a prolonged recuperative phase before regaining functional status, with attendant need for intensive nursing care. In a recent study of CCSM dogs treated via dorsal laminectomy, 71% worsened neurologically two days after surgery, and the mean time to attain optimal neurologic function was 3.6 mo. Nonambulatory dogs took an average of 2.5 mo to regain ambulatory ability. Nevertheless, 95% of the dogs undergoing dorsal laminectomy had a good eventual outcome. In comparison, postoperative morbidity for distraction-stabilization techniques has been reported as 12% or less. Although dogs undergoing distraction-stabilization procedures tend not to worsen neurologically after surgery to the extent exhibited by dogs undergoing dorsal laminectomy, prolonged recuperation is often required for these patients as well. Dogs who present nonambulatory and/or have more than one lesion on myelography tend to have a less favorable prognosis than ambulatory dogs and dogs having only one demonstrable lesion. In general, dogs with caudal cervical spondylomyelopathy who are ambulatory at presentation and have myelographic and/or CT/MR evidence of a single affected intervertebral space have a favorable prognosis for functional recovery. The recurrence rate for CCSM has been reported to be 22–28%.

3. Degenerative myelopathy^{1,76–83}

- a. This is a degenerative disease of unknown etiology primarily affecting the thoracolumbar spinal cord of medium- to large-breed dogs over 5 yr of age. The German shepherd dog is by far the most common breed affected, but other dog breeds and one cat have been reported with this disease. Two young German Shepherd dogs (6–7 mo old) have recently been reported with a disease process consistent with degenerative myelopathy. Pathologically, there is loss of myelin and axons throughout the spinal cord, which is often asymmetrical, and mainly in the thoracic spinal cord region. Associations between low serum levels of certain vitamins (Vitamins B₁₂ and E) have been made in some German Shepherd dogs with degenerative myelopathy. There is also some evidence to suggest an immune-mediated basis for this disease.
- b. The clinical picture typically consists of a slowly progressive, nonpainful T3–L3 myelopathy in a middle-aged to older large-breed dog, usually of the German Shepherd breed. Loss of pelvic limb proprioceptive ability (ataxia, toe-dragging) is noticed initially, followed by gradual loss of voluntary motor function. Spinal reflexes in the pelvic limbs are typically normal to hyperreflexive. Decreased to absent patellar reflexes are found in approximately 10%–15% of patients, however, and may reflect selective damage to dorsal lumbar nerve roots in these dogs. The disease usually progresses over a 6–12-mo period, at which time most owners elect for

euthanasia, due to the nonambulatory status of the affected patient. The disease can progress to involve the thoracic limbs and eventually the brain stem in dogs kept alive after this degree of deterioration.

- c. A tentative diagnosis is based upon signalment, clinical features, and exclusion of other spinal cord disorders. Patients with degenerative myelopathy typically have normal CSF results, or increased protein levels with a normal cell count. The myelogram is typically normal, but some dogs may have concurrent mild Type II disk lesions that are probably clinically insignificant. A definitive diagnosis is based upon characteristic histopathologic lesions in the spinal cord at necropsy.
 - d. Exercise, vitamin supplementation, glucocorticoid administration, and treatment with the protease inhibitor, aminocaproic acid, have all been advocated as potential therapies. However, none of these treatments has been shown to alter the progression of the disease. The long-term prognosis is poor, and most dogs are euthanized due to severe pelvic limb dysfunction within 6–12 mo.
4. Extradural synovial cysts^{84,85}
- a. In two recent reports, a total of six dogs were described in which single or multiple protrusions of cystic synovial tissue from the intervertebral articular facet joints resulted in clinical signs of myelopathy. These protrusions were dorsolateral, primarily causing an axial deviation of the spinal cord. Five of the six cases were young adult (1–2 yr of age), male, giant-breed dogs (four Mastiffs, one Great Dane). The sixth dog was a 10-yr-old, female, German shorthaired pointer. The etiology of this disorder is unknown, but is most likely associated with degenerative change in the articular facet joint, with subsequent protrusion of synovium through a weakened joint capsule.
 - b. In all but one of six dogs (the pointer), clinical signs of a progressive cervical myelopathy were evident. The pointer exhibited signs of a progressive T3–L3 myelopathy. The onset and progression of clinical signs of myelopathy were described as “relatively short” in one report and occurring over at least four months in the other report.
 - c. A definitive histopathologic diagnosis was achieved in all six dogs. Degenerative changes in the facet joints were evident on plain radiography, and myelography typically revealed axial deviation of the spinal cord by the cystic structures, best visualized on ventrodorsal views. CT or MR imaging may also be used to diagnose extradural synovial cysts (Fig. 9.14). A consistent CSF finding for this disorder is elevated protein levels with normal cell count, but one dog had a mild, mixed-cell pleocytosis.
 - d. Surgical treatment of this disorder involves laminectomy and removal of the compressive synovial cyst(s). A dorsal laminectomy was performed in each of the five cervical cases, and a hemilaminectomy was performed for the dog with thoracolumbar myelopathy. The prognosis for recovery with surgical management appears to be excellent. Five of the six dogs became

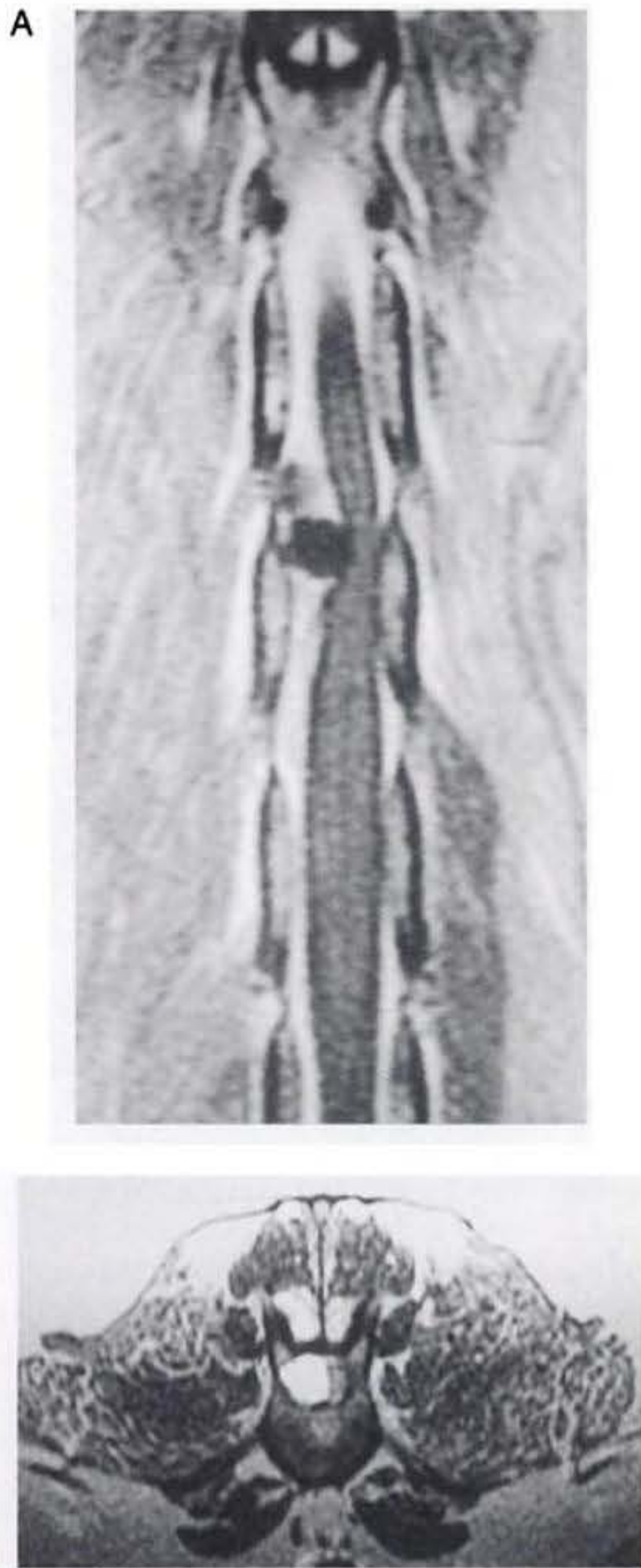


Fig. 9.14. Dorsal T1-weighted (A) and transaxial T2-weighted (B) images of a dog's lumbar spine, showing an extradural synovial cyst (Courtesy of Dr. Jason Berg).

asymptomatic following surgery. The remaining dog had become nonambulatory following surgery, but subsequently recovered ambulatory function.

5. Rottweiler leukoencephalomyelopathy^{1,76,86–89}
 - a. This is a progressive, nonpainful demyelinating disease of unknown etiology reported in young adult (1.5–4 yr of age) Rottweilers and a Rottweiler cross-bred dog. This disease is classified as a leukodystrophy, a CNS white matter disorder characterized by abnormal myelin synthesis and/or maintenance. The mode of inheritance is suspected to be autosomal recessive.
 - b. Clinical signs are suggestive of a slowly progressive cervical myelopathy. Hypermetria is often more pronounced in the thoracic limbs, while conscious proprioceptive deficits are often more obvious in the pelvic limbs. The tetraparesis slowly worsens over 6 to 12 mo.
 - c. A tentative diagnosis is based upon signalment, history, clinical signs, and ruling out other causes of cervical myelopathy with appropriate diagnostic tests. Results of CSF analysis, radiography/myelography, and electrodiagnostic studies are normal with this disease. Histopathologically, symmetrical demyelinating lesions are seen in the spinal cord (especially cervical), brain stem, optic nerves and tracts, and the cerebellum. Despite the cerebellar lesions, these dogs typically do not exhibit classical features of cerebellar dysfunction. In another disease of Rottweilers, neuroaxonal dystrophy, clinical signs of cerebellar dysfunction are common; neuroaxonal dystrophy is discussed in Chapter 8.
 - d. There is no effective treatment available for this disease and the prognosis for recovery is poor.
6. Afghan hound hereditary myelopathy^{1,76,78,90–93}
 - a. A rapidly progressive leukodystrophy has been described in young (3- to 13-mo-old) Afghan hounds with an autosomal recessive mode of inheritance.
 - b. Clinical signs are initially consistent with either a C6–T2 or a T3–L3 myelopathy. These patients typically present with a symmetrical paraparesis, and may display a “bunny-hopping” gait. Within 1–3 wk, these dogs become paraplegic and some may become tetraparetic or tetraplegic. Respiratory dysfunction can subsequently occur and lead to death, if euthanasia is not performed prior to this development.
 - c. Other than elevated CSF protein levels in some dogs with this disease, results of diagnostic tests are normal. A tentative diagnosis is based upon signalment and clinical findings. Histopathologically, there is bilaterally symmetrical vacuolation of spinal cord white matter with extensive myelin loss from caudal cervical to lower lumbar segments. There may be lesions in the brain-stem area, but there is no clinical evidence of brain-stem disease.
 - d. There is no treatment for this disease and the prognosis is poor. A similar disorder has been reported in Dutch Kooiker dogs.
7. Other leukodystrophies^{76,78,94}

- a. Leukodystrophies resulting in clinical signs of spinal cord dysfunction have been reported in young Dalmatians and Miniature Poodles. A rare disorder called fibrinoid leukodystrophy has been sporadically reported in a number of young dogs. Dogs with this latter disease typically show signs of brain and spinal cord dysfunction. Histologically, astrocytic inclusion bodies, called Rosenthal fibers, are seen in dogs with fibrinoid leukodystrophy.
- b. No treatments are available for these progressive diseases, and prognosis is poor.
- 8. Hereditary ataxia of Jack Russell and Smooth Fox terriers^{76,95,96}
 - a. This is a rare, autosomal recessive disorder in which spinal cord axons and myelin in the cervical and thoracolumbar areas undergo progressive degeneration. Lesions in central auditory pathways have also been described.
 - b. Clinical signs begin with pelvic limb ataxia at 2–6 mo of age, and eventually all four limbs are affected. The dysmetric gait and occasional intention tremor are more suggestive of cerebellar dysfunction than a myelopathy. There is no clinical evidence of hearing impairment.
 - c. The prognosis is guarded. The disease is very slowly progressive and may stabilize. Affected animals may have a good quality of life, despite the gait abnormalities. A similar pathologic condition has been described in Ibizan hounds. Focal or generalized seizures have been observed in these latter dogs, however.
- 9. Labrador retriever axonopathy^{76,97}
 - a. This is a recently described degenerative disease of young (3- to 4-week-old) Labrador retrievers, presumably of autosomal recessive inheritance. Progressive axonal degeneration occurs throughout the spinal cord, as well as in the brain stem and cerebellum. Abnormal development of the corpus callosum is a consistent feature.
 - b. Clinical signs begin with pelvic limb ataxia and paresis that rapidly progresses to a dysmetric tetraparesis. Some dogs display intention tremors. Most dogs cannot rise without assistance by 3–5 mo of age. Signs are suggestive of cerebellar and spinal cord disease.
 - c. Most dogs progress to a nonambulatory status by 5 mo of age. There is no effective treatment and the prognosis is poor.
- 10. Lysosomal storage diseases
 - a. Lysosomal storage disorders typically cause signs of a progressive multifocal encephalopathy and/or myelopathy in a young (2- to 6-mo-old) animal. Occasionally, clinical signs of a progressive myelopathy predominate. Examples are globoid cell leukodystrophy (Krabbe's disease) in dogs and mucopolysaccharidosis in cats. Lysosomal storage diseases are discussed in Chapter 4.
 - b. The prognosis is poor in most cases. Sometimes, decompressive surgery in cases of mucopolysaccharidosis (with malformed vertebrae impinging on the spinal cord) will be successful.

11. Motor neuron diseases

While this group of diseases technically falls under spinal cord disorders, they result in lower motor neuron signs and will be discussed in Chapter 12.

B. Anomalous/developmental

1. Congenital vertebral malformations^{1,98-103}

- a. Many vertebral malformations are discovered incidentally and do not cause clinical problems. Some malformations may lead to spinal cord damage and clinical signs of dysfunction by static or progressive (i.e., as the patient grows into adulthood) spinal stenosis, and/or vertebral instability caused by the abnormal vertebra or vertebrae. The commonly reported vertebral malformations are:

- (1) Hemivertebra (Fig. 9.15)—part of the vertebra fails to form properly, usually the vertebral body. The abnormal vertebra usually has a wedge shape. If the central part of the vertebra fails to form, a type of hemivertebra called butterfly vertebra may result. Hemivertebrae are seen most commonly in the screw-tail breeds (e.g., Bulldogs, Boston terriers, etc.).

A



B



Fig. 9.15. Lateral plain radiographic (A) and myelographic (B) images of a dog with a hemivertebra in the thoracic spine, leading to kyphosis and spinal cord compression.

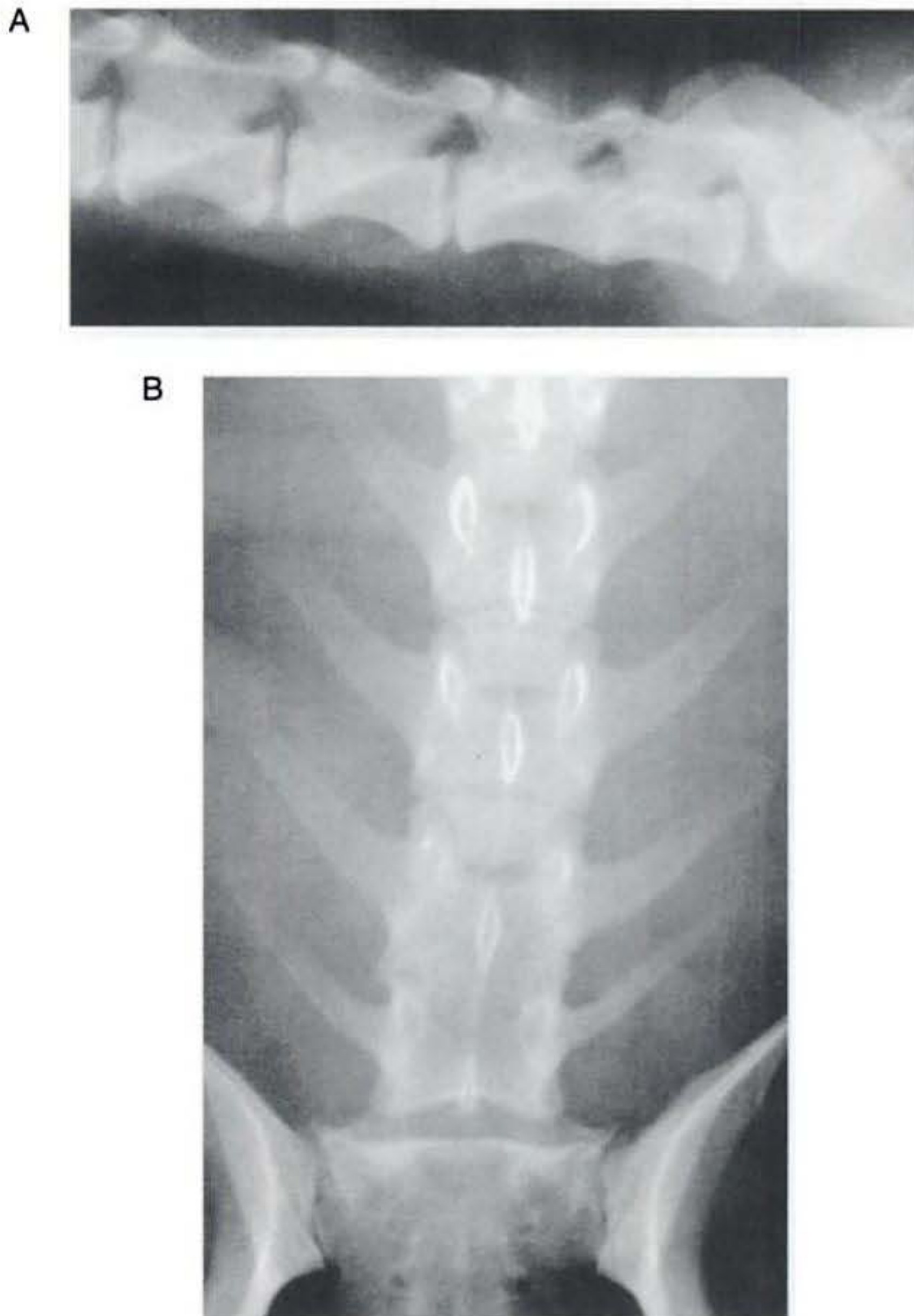


Fig. 9.16. Lateral (A) and ventrolateral (B) radiographic views of a dog with a block vertebra in the lumbar (L6–L7) spine (Courtesy of Dr. Mike Walker).

- (2) Block vertebra (Fig. 9.16)—this is a failure of segmentation leading to a combined vertebra, composed of what should have been two or more single vertebrae.
- (3) Spina bifida (Fig. 9.17)—this refers to a failure of fusion of the dorsal parts of the vertebra. This may occur alone and cause no clinical signs



Fig. 9.17. Ventrodorsal radiograph of a dog with spina bifida of a thoracic vertebra.

of dysfunction, but is often associated with meningeal and/or spinal cord malformations (e.g., meningocele, myelomeningocele). English bulldogs and Manx cats appear to be predisposed to this disorder.

- (4) Stenotic vertebral canal—this can occur in association with other anomalies (e.g., hemivertebra) or as an isolated vertebral malformation. Relative stenosis refers to canal narrowing that does not cause compression of neural tissue, whereas absolute stenosis means that the stenosis does compress parenchymal tissue. Doberman Pinschers often have a relative stenosis of the cranial thoracic vertebrae (usually T3–T6). Absolute stenosis of cervical vertebrae has been described in Bassett hounds, Doberman Pinschers, and Great Danes.
- (5) Transitional vertebra (Fig. 9.18)—this describes a vertebra that has shape characteristics of two different vertebral types. The most common examples are “lumbarization” of the sacrum or “sacralization” of the last lumbar vertebra. The clinical significance of these vertebrae will be discussed in Chapter 10.

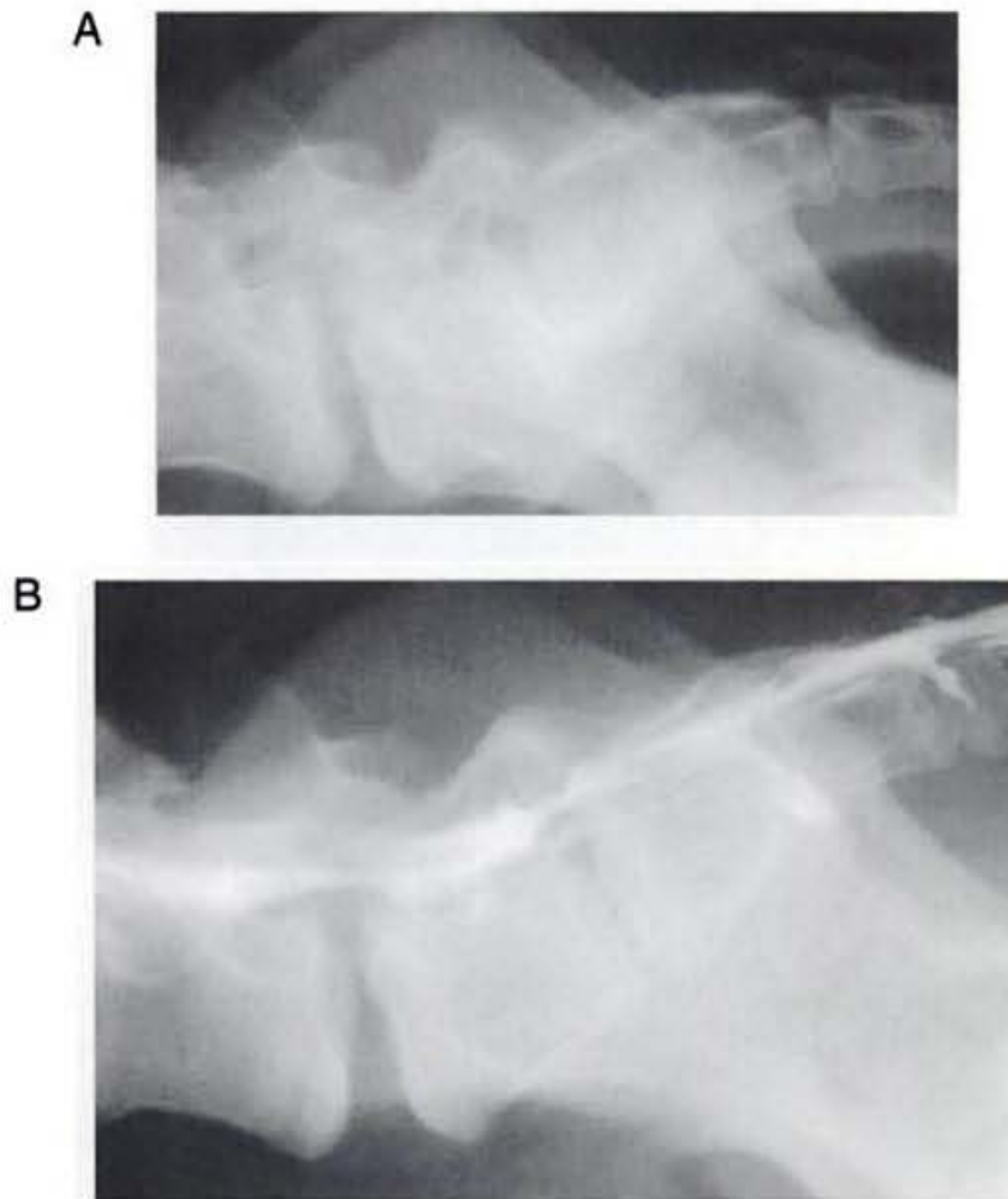


Fig. 9.18. Lateral radiograph of the lumbosacral region of a dog, before (A) and after (B) epidurography. A transitional vertebra (lumbarization of the sacrum is evident (Courtesy of Dr. Mike Walker).

- (6) Atlantoaxial instability (Fig. 9.19)—this is usually caused by hypoplasia or aplasia of the dens. Abnormal ligamentous support of the dens may also be involved. This problem is usually seen in miniature and toy dog breeds, less than one year of age, but has been reported in adult dogs and larger dog breeds. It occasionally occurs in cats. The instability may lead to dorsal subluxation or luxation of the axis, with resultant compression of the cranial cervical spinal cord. Associated malformations of the atlas and/or occipital bones may be observed in some patients.
- b. Clinical signs, if present, associated with the above malformations should correspond to the anatomic location of the abnormality. In most cases, the clinically affected patient is an immature animal, but some patients may not exhibit clinical signs until adulthood. Onset of clinical signs of dysfunction may be acute or chronic. Depending on the specific abnormality or abnormalities, clinical signs may or may not progress. In some cases, clinical signs of dysfunction are intermittent. In the case of atlantoaxial



Fig. 9.19. Lateral radiograph of a dog's cranial cervical spine, demonstrating instability at the atlantoaxial joint.

- instability, clinical signs can vary from neck pain with no neurologic deficits to tetraplegia with respiratory difficulty.
- c. Diagnosis of a vertebral malformation as a cause of clinical disease is based upon signalment, history, and neurologic deficits that match the location of the abnormality. Plain radiography and myelography are often used in diagnosis. Stressed views may be used to demonstrate atlantoaxial instability, but they must be performed with caution. Overzealous flexion of the neck to demonstrate instability of the C1–C2 joint space may have disastrous results in these patients. Another, potentially safer method of diagnosing atlantoaxial instability in dogs is via CT or MR imaging.
 - d. Treatment of patients with vertebral malformations that cause clinical signs of dysfunction is often frustrating, but some cases may respond to medical therapy (e.g., anti-inflammatory doses of glucocorticoids) or surgical stabilization with or without decompression. Atlantoaxial instability is sometimes treated with glucocorticoids and external splinting of the neck, but most of these dogs eventually require surgical stabilization. The surgical technique recommended by the author involves a ventral approach with cancellous bone grafting and stabilization with pins and polymethylmethacrylate (PMMA) (Fig. 9.20). A dorsal approach which involves securing the atlas to the axis with orthopedic wire or suture is also commonly performed. The prognosis for most of the vertebral malformations that cause signs of dysfunction is guarded. The prognosis for patients with atlantoaxial instability is fair to good if there are mild to moderate neurologic deficits, and guarded if the deficits are severe (e.g., tetraplegia). In a recent report, 87% of dogs with atlantoaxial instability undergoing surgical stabilization survived the surgical procedure. Postoperative complications involving upper respiratory function (e.g., coughing, gagging, laryngeal paralysis) occasionally occur with the ventral approach.

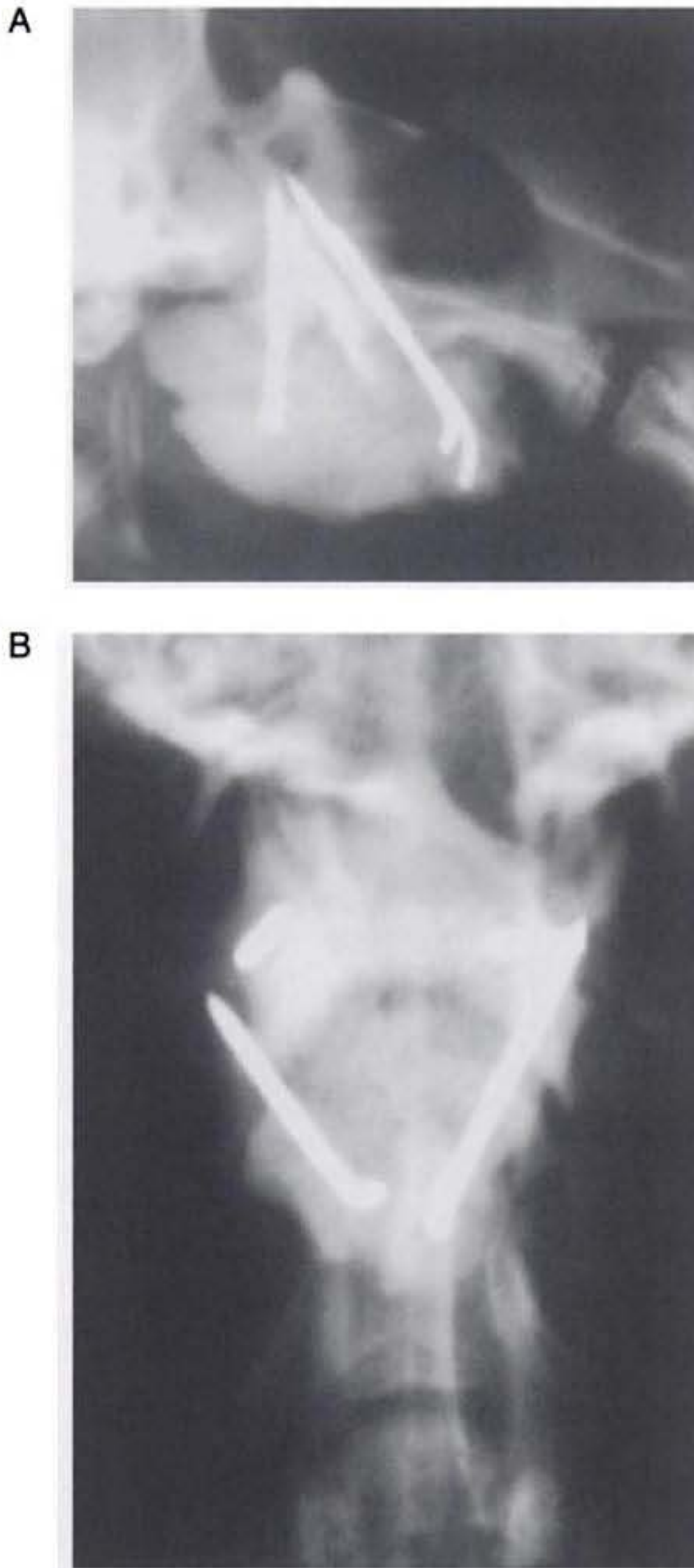


Fig. 9.20. Lateral (A) and ventrodorsal (B) postoperative radiographs of an atlantoaxial instability lesion corrected with pins and PMMA.

2. Stenotic vertebral canal^{1,98}

In contrast to the congenital condition, this is progressive until skeletal growth is completed. This may be due to inborn errors of skeletal growth or other as yet unidentified factors. The stenosis can be relative or absolute, similar to the congenital condition.

3. Cartilaginous exostoses^{1,98,104-112}

- a. Also known as osteochondroma/osteochondromatosis, this is an uncommon condition in which nodules of cartilage, with or without bone, proliferate in the growth plate areas of various bones. The vertebrae, ribs, and long bones of the limbs are most frequently affected. Multiple lesions (multiple cartilaginous exostoses or MCE) are seen most commonly, but solitary growths occasionally occur. This disease typically occurs in young dogs and adult cats. There is some evidence that this is a heritable condition in dogs. In cats, MCE has been associated with the feline leukemia virus (FeLV).
- b. Clinical signs of myelopathy occur when exostoses of the vertebrae impinge on the spinal cord. Most dogs with MCE affecting the spinal cord are presented for clinical signs of myelopathy before 1 yr of age. However, dogs with MCE may be young adults (more than 1 yr old) by the time the mass or masses result in clinical signs of disease. Some dogs may develop neurologic dysfunction at an older age, due to neoplastic transformation of one or more exostoses. Cats with MCE tend to be adults at the time clinical signs of myelopathy are evident. The clinical signs depend upon the region(s) of the spinal cord that is(are) compressed.
- c. A tentative diagnosis is made via visualizing the characteristic lesions on spinal radiographs (Fig. 9.21). Definitive diagnosis is attained via histopathologic examination of the nodules.
- d. Prognosis with surgical resection in a skeletally mature dog has traditionally been regarded as generally good, because growth of exostoses was thought to be arrested at the time of skeletal maturity. However, recent investigation into this disease in dogs suggests that progressive growth of

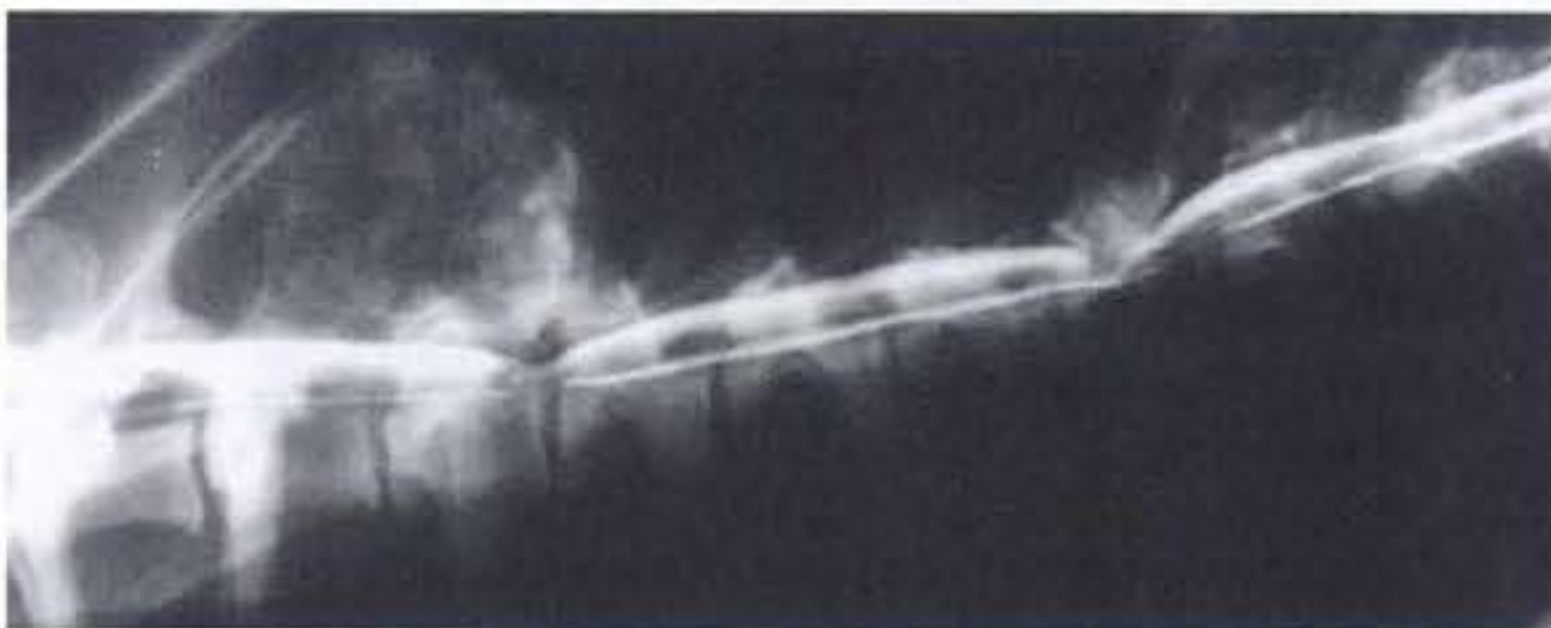


Fig. 9.21. Lateral myelographic image of a dog with multiple cartilaginous exostoses of the thoracic spine.

exostoses after skeletal maturity may be more common than previously believed, warranting a guarded to poor prognosis. The disease is considered aggressive in cats, and has a poor prognosis. Malignant transformation of exostoses in adult animals has been described. Such transformation may also be more common in dogs than previously appreciated, sometimes occurring several years after diagnosis of cartilaginous exostoses.

4. Meningoceles/myelomeningoceles

Meningoceles and myelomeningoceles are protrusions of meninges and CSF, with or without parenchymal tissue, respectively. They are often associated with spina bifida. They occur most commonly in the lumbosacral region and will be discussed in Chapter 10.

5. Spinal dysraphism^{1,113-120}

- a. Myelodysplasia is a “catchall” term that refers to a number of abnormalities of embryological development, including duplication and absence of cord structures, as well as syringomyelia and hydromyelia. A specific form of myelodysplasia, referred to as spinal dysraphism, is thought to be a hereditary disease in Weimaraner dogs. This condition occasionally occurs in other dog breeds. Most of the abnormalities are located along the median plane of the spinal cord in these dogs.
- b. Clinical signs of a T3–L3 myelopathy are usually apparent by 4–6 wk of age. A “bunny hopping” pelvic limb gait is the most characteristic feature of spinal dysraphism. Proprioceptive deficits in the pelvic limbs are also common, whereas paraparesis is uncommon. The condition is also typically nonprogressive, even when hydromyelia/syringomyelia is present.
- c. A tentative diagnosis of spinal dysraphism is made primarily based upon signalment, history, and clinical signs. Results of diagnostic tests (e.g., CSF analysis, radiography, myelography, CT, MRI) are typically normal, depending upon the specific spinal abnormalities and the specific tests performed (e.g., hydromyelia/syringomyelia may not be apparent on myelography, but will likely be visible with MRI).
- d. There is no treatment for spinal dysraphism. Since the clinical signs are usually not severe, and the disorder is not progressive, the prognosis for life as a functional pet is good.

6. Hydromyelia/syringomyelia^{1,113,121-141}

- a. Hydromyelia is a fluid dilatation of the central canal and syringomyelia is a fluid dilatation within the spinal cord outside the central canal that may or may not communicate with the central canal. Distinguishing between hydromyelia and syringomyelia is often impossible in the living patient and is clinically unimportant. Hydromyelia/syringomyelia may be associated with other congenital spinal cord (e.g., spinal dysraphism) and/or brain (e.g., Dandy-Walker syndrome, hydrocephalus) malformations, but may also be caused by inflammatory and neoplastic processes that obstruct the flow of CSF. It can also occur secondary to spinal cord trauma. This

condition can also occur as a solitary disorder of an unknown etiology (idiopathic).

In human beings, the majority of hydromyelia/syringomyelia cases are associated with abnormalities of the caudal medullary/cerebellar region of the brain, such as Chiari Type I malformation (most commonly), intra-arachnoid cysts, and Dandy-Walker syndrome. It is believed that these hindbrain anomalies are not merely coincidental malformations that occur concomitantly with hydromyelia/syringomyelia, but that they may actually cause the hydromyelia/syringomyelia by disrupting normal CSF flow mechanisms. In a recent report, seven Cavalier King Charles spaniels with hydromyelia/syringomyelia were described. Caudal fossa abnormalities, similar to human Chiari Type I malformations were associated with the development of hydromyelia/syringomyelia in those dogs. The author has encountered a number of small-breed dogs with hydromyelia/syringomyelia and Chiari-like malformations of the caudal fossa; the majority of these dogs have been toy and miniature Poodles.

- b. Clinical signs of a myelopathy may be acute or chronic and may or may not be progressive. In the majority of reported cases, onset of clinical signs of neurologic dysfunction occurred in adulthood. The age range of clinical disease onset is very broad, possibly reflecting the multitude of suspected etiologies for the condition. This age range may also reflect different rates of fluid accumulation and subsequent spinal cord dysfunction among dogs. Scoliosis, especially of the cervical region (i.e., torticollis) and spinal hyperesthesia are frequent clinical findings in cases of hydromyelia/syringomyelia. The development of scoliosis has been proposed to be due to asymmetric damage to lower motor neurons that supply epaxial/hypaxial musculature caused by the accumulated fluid. An alternative hypothesis is that the scoliosis is a sensory phenomenon due to asymmetric damage to dorsal horn grey matter by the accumulated fluid (A. de Lahunta, personal communication). Proprioceptive deficits and limb paresis also occur with some frequency.

Persistent scratching at the neck and shoulder area on one side was the initial clinical sign in all seven of the reported King Charles spaniels with hydromyelia/syringomyelia. Clinical signs of neurologic dysfunction progressed in all dogs. Spinal and limb-associated hyperesthesia, as well as unilateral thoracic limb LMN dysfunction, were frequent findings in these patients.

- c. Diagnosis may be difficult with myelography. Occasionally during myelography, the contrast medium will enter the central canal (canalogram) and provide a diagnosis. More often, however, the spinal cord will either appear subjectively wider than normal, or normal on myelography. Computed tomography or MRI are much more likely to demonstrate the cavitory lesions. The author prefers MR imaging for dogs suspected to have hydromyelia/syringomyelia, as this imaging modality is more likely to iden-

tify Chiari-like malformations (sagittal view) as well as the fluid-filled spinal cord lesions (Fig. 9.22). Cerebrospinal fluid is often either normal or indicative of mild inflammation in most cases of hydromyelia/syringomyelia; CSF should be evaluated to help rule out potential underlying causes (e.g., inflammatory/infectious disease).

- d. There is little information available concerning treatment of this disorder in dogs and cats. Medical therapy, consisting of glucocorticoids +/- acetazolamide administration (see Hydrocephalus, Chapter 4) may be successful in some cases. Surgical drainage and shunting is often successful in people with this disorder. Foramen magnum decompression (FMD), with or without shunting, is also commonly performed in those people who have evidence of a hindbrain anomaly as a potential cause of the hydromyelia/syringomyelia. For Chiari malformation-associated disorders, FMD alone is very successful.

There are three reports of surgical management of hydromyelia/syringomyelia in dogs, all of which were unsuccessful. In one case, a ventriculoperitoneal shunt was placed (the dog also had hydrocephalus), but the rostral end of the shunt was improperly placed. In another case, a dorsal laminectomy was performed over the lesion, but no fluid drainage was attempted; the dog never regained ambulatory status. In the third case, the syrinx was incised and drained, but a second fluid cavity developed and caused neurologic dysfunction shortly after surgery. The author recently performed FMD with dura/arachnoid excision in two dogs with Chiari-like malformation and hydromyelia/syringomyelia; the outcome was favorable in both cases.

The prognosis for dogs and cats with hydromyelia/syringomyelia is considered guarded, but this is based on only a few cases in which treatment was attempted. Hopefully, with the increased availability of advanced imaging, more meaningful data on treatment success for this disease syndrome will become available.

7. Pilonidal sinus (dermoid sinus)^{1,142}
 - a. A failure of separation of the neural tube from the skin ectoderm during embryogenesis is believed to be the basis for this disorder. A sinus tract with a small cutaneous opening on the dorsal midline extends ventrally to various depths, sometimes to the level of the subarachnoid space. This is encountered most commonly in Rhodesian Ridgeback dogs, but has been reported in other breeds. The sinus is most often located in the cervical, cranial thoracic, and sacrocaudal regions, but can occur anywhere along the spine. The sinus tract is lined with squamous epithelium and adnexa (hair follicles and sebaceous glands). Pilonidal sinus is thought to be a heritable condition (suspected to be autosomal recessive in ridgebacks).
 - b. Clinical signs may vary from irritation due to bacterial infection of the sinus (most commonly), to evidence of meningitis and myelitis in cases

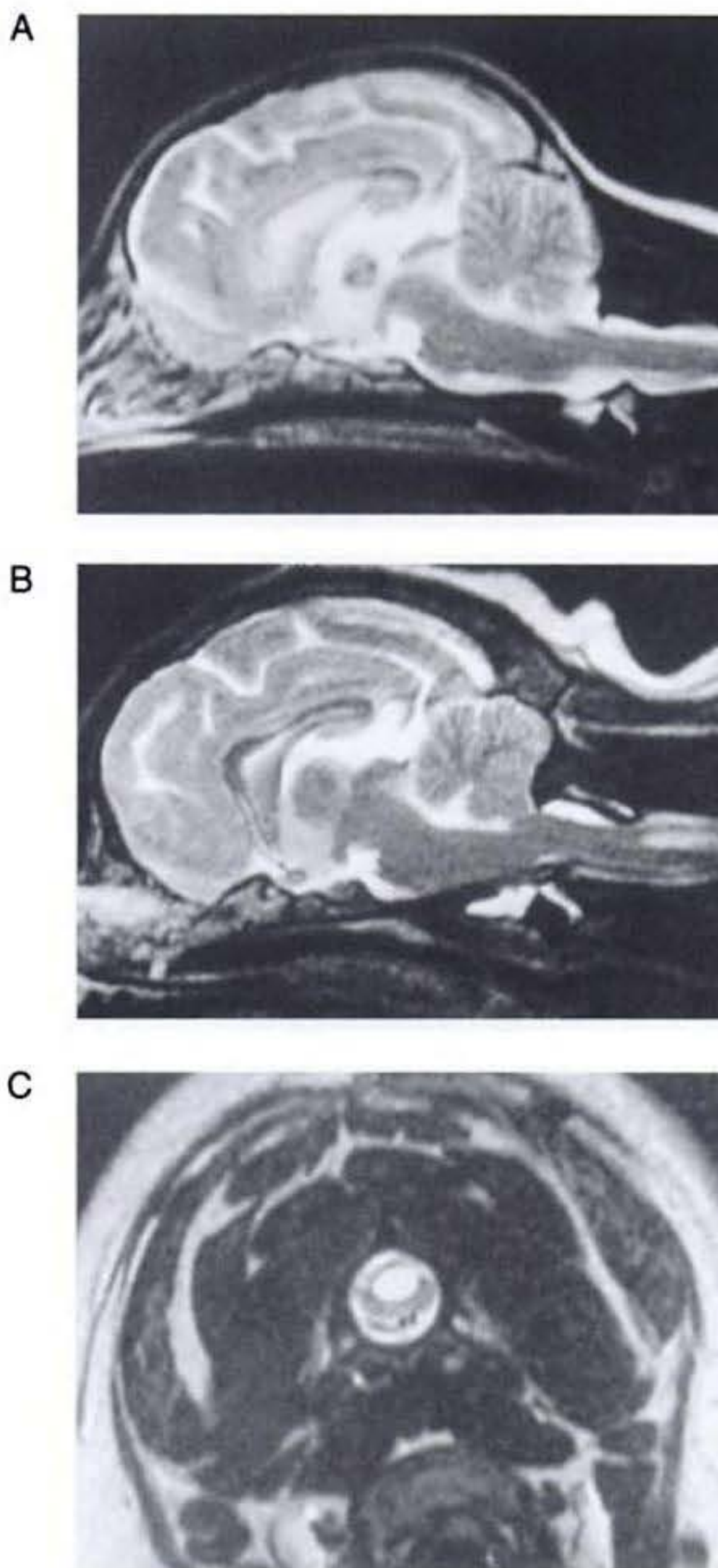


Fig. 9.22. Sagittal MR images (T2-weighted) of a small-breed dog with normal caudal fossa anatomy (A), and a small-breed dog with Chiari-like malformation of the caudal fossa (B). Abnormalities evident in image (B) include rostral indentation of the caudal cerebellum by the occipital bone and obliteration of the dorsal subarachnoid space at the cervicomedullary junction. A transaxial T2-weighted MR image of the second dog's cervical spine (C) demonstrates hydromyelia/syringomyelia of the spinal cord.

that involve sinus communication with the meninges and spinal cord.

Onset of clinical signs usually occurs at a young age, but can occur at any age. A thick fibrous cord (the sinus) can often be palpated subcutaneously on the dorsal midline.

- c. Diagnosis is based upon signalment, history, clinical signs, and demonstration of a sinus tract via fistulography. Myelography may also be used to demonstrate or rule out communication of the sinus with the subarachnoid space. Contrast sinus fistulograms should be performed with agents that are safe to use for myelography, if communication of the sinus with the subarachnoid space is suspected or known.
 - d. Treatment includes broad-spectrum antibiotics based upon culture and sensitivity results, and complete surgical excision of the sinus tract. Prognosis varies with the extent of neurologic dysfunction (if any) and whether or not the entire sinus tract is successfully removed. In general the prognosis is guarded to good.
8. Spinal arachnoid cysts^{1,143–147}
- a. The name for this uncommon disorder is a misnomer, because the lesions are actually CSF-filled diverticuli of the subarachnoid space, rather than true cysts. Proposed causes of these anomalous fluid accumulations are numerous, including congenital malformation, trauma, inflammation (arachnoiditis), and neoplasia. However, an underlying etiology is rarely found for spinal arachnoid cysts. The accumulated fluid causes compression of adjacent spinal cord parenchyma, resulting in clinical signs of myelopathy. Spinal arachnoid cysts are typically solitary, focal accumulations of fluid that occur at either the cranial cervical or caudal thoracic regions of the spinal cord.
 - b. With the exception of two cats, all spinal arachnoid cysts have been reported in dogs. The age at onset of clinical signs of neurologic dysfunction is quite variable, with most dogs developing signs of myelopathy in adulthood. In one report, the mean age at onset of clinical signs was 8 mo and in another it was 4.5 yr. The author treated two dogs with spinal arachnoid cysts that developed clinical signs of myelopathy at 7 yr of age. Clinical signs typically correspond to either a C1–C5 or T3–L3 myelopathy, and are usually chronic and progressive.
 - c. The diagnosis of spinal arachnoid cyst is based primarily on spinal imaging; myelographic diagnosis of spinal arachnoid cysts is most commonly reported, but both CT and MR imaging (Fig. 9.23) have also been successfully used. The typical myelographic appearance is a bulbous, contrast-filled diverticulum continuous with the contrast column of the subarachnoid space. CSF analysis is usually within normal limits. Histopathology of resected “cyst wall” reveals meningeal tissue (dura-arachnoid).
 - d. Medical management (i.e., glucocorticoid therapy) may be attempted, but is unlikely to be successful in the long term. Surgical management involves resecting a portion of the meninges comprising the “cyst” wall,



Fig. 9.23. Sagittal T1-weighted image of the cervical spine, demonstrating a spinal arachnoid cyst in a dog.

thereby relieving the pressure exerted on the underlying spinal cord parenchyma. From the limited data available, surgical treatment of spinal arachnoid cysts in dogs and cats appears to have a good prognosis.

C. Neoplastic^{1,148-184}

1. There are a large number of tumors that can affect the spinal cord of dogs and cats. As with brain tumors (see Chapter 4), tumors affecting the spinal cord can be conceptually divided into primary and secondary tumors. Primary tumors include those neoplasms that arise from spinal cord parenchyma (e.g., neurons, glial cells), or associated meningeal/ependymal tissue. Secondary tumors include primary or metastatic vertebral neoplasms, malignant nerve sheath tumors (MNST—see Chapter 12 also), and metastases to the extradural space or the cord parenchyma (intramedullary metastases). As with brain tumors, primary tumors are more common than metastatic tumors. It is often clinically useful to classify spinal cord neoplasms based upon the relationship between the tumor and the meninges. Spinal cord tumors may be classified as extradural, intradural/ extramedullary, or intramedullary (see Chapter 3). Spinal cord tumors exert their pathologic effects by compression and/or invasion of the spinal cord, as well as producing peritumoral edema, inflammation, and hemorrhage. Examples of some of the more commonly encountered spinal cord tumors in dogs and cats are as follows:
 - a. Extradural tumors—this category includes primary and metastatic vertebral and soft tissue tumors. Primary vertebral tumors such as osteosarcoma, chondrosarcoma, myeloma (plasma cell tumor), fibrosarcoma, and hemangiosarcoma are the most common extradural tumors encountered in dogs. It may be difficult in some cases to ascertain whether a vertebral tumor is primary or metastatic. Other tumors may occur in the epidural space, without directly involving the vertebrae. Lymphosarcoma can be primary or metastatic, and is typically located in the extradural space. Lymphosarcoma is the most common spinal tumor of cats. Meningioma and MNST usually are typically located intradurally, but occasionally will exhibit an extadural pattern on myelography. Metastatic carcinomas (e.g.,

mammary carcinoma, prostatic carcinoma) may localize to the extradural space. Extradural tumors represent the most frequently diagnosed category of spinal neoplasia.

- b. Intradural/extramedullary tumors—meningiomas and MNSTs are the two most common neoplasms in this category. An uncommon blast-cell tumor (BCT) of young dogs also typically displays an intradural/extramedullary myelographic pattern. Spinal tumors exhibiting this myelographic pattern represent the second most common category of spinal neoplasia.
 - c. Intramedullary tumors—these infrequently encountered neoplasms include primary spinal parenchymal tumors (e.g., astrocytoma, oligodendroglioma, ependymoma) and intramedullary metastases. The most common intramedullary metastases in dogs are thought to be hemangiosarcoma and lymphosarcoma.
2. In general, most patients with spinal neoplasia are older (e.g., more than 5 yr), but some tumors (lymphosarcoma, blast-cell tumors) are seen commonly in young animals. The median age of cats with spinal lymphosarcoma is 2–3 yr. Blast-cell tumors in dogs are typically diagnosed between 6 mo and 3 yr of age. These uncommon neoplasms have been ascribed multiple names, including neuroepithelioma, medulloepithelioma, ependymoma, and neuroblastoma. It is unlikely that this neoplasm is an ependymoma, but very likely that it is a neuroblastoma. German Shepherd dogs and retrievers appear to be predisposed to developing blast-cell tumors. Large-breed dogs appear to be predisposed to developing spinal neoplasia, in comparison with smaller breeds.

Spinal tumors classically cause progressive signs of a myelopathy, but acute or subacute development of spinal cord dysfunction often occurs, especially with feline lymphosarcoma and intramedullary neoplasms. Rapid onset of clinical signs may be due to such factors as pathologic fracture of a cancerous vertebra, acute hemorrhage or necrosis of a tumor, or rapid growth of a neoplasm with subsequent damage to spinal cord parenchyma (more likely with intramedullary tumors). Spinal cord tumors are typically solitary, and can occur anywhere along the length of the spine. Meningiomas and MNSTs arise most frequently in the cervical spinal cord, with MNSTs being especially prominent in the cervical intumescence area. Feline lymphosarcoma is found more often in the thoracolumbar spine than the cervical spine. All reported BCTs of young dogs have been located between T10 and L2 vertebral levels.

A prominent feature of extradural and intradural/extramedullary spinal neoplasia is spinal hyperesthesia, which often precedes the onset of proprioceptive and voluntary motor deficits. Spinal hyperesthesia is often not a prominent early clinical feature in patients with intramedullary spinal tumors, probably due to the lack of meningeal involvement. In MNSTs of the cervical intumescence, a history of unilateral thoracic limb lameness (on the side of the tumor) preceding the development of clinical signs of myelopathy is common.

3. A tentative diagnosis of spinal neoplasia is typically based upon signalment, history, clinical signs, and results of spinal imaging. Bloodwork abnormalities are unlikely, but hyperglobulinemia and proteinuria may be evident in cases of myeloma. Most cats with spinal lymphosarcoma are FeLV positive, have leukemic bone marrow, and have multicentric neoplasia. With the possible exception of spinal lymphosarcoma, CSF evaluation rarely reveals neoplastic cells, and may reveal increased protein levels, with or without elevated cell counts (more likely with tumors with meningeal involvement). In cases of vertebral neoplasia, bony lysis with loss of cortical outlines is often seen on imaging of affected vertebrae, with or without evidence of bony proliferation (Fig. 9.24). In the majority of soft tissue spinal neoplasms, plain radiographs of the spine are normal. Myelography, CT, or MR imaging (Fig. 9.25) are usually helpful both in diagnosis of spinal tumors and therapeutic planning. An intramedullary myelographic pattern may be misleading, as an intradural/extramedullary mass with attendant cord swelling may cause an identical myelographic pattern. Intradural/extramedullary spinal tumors will occasionally infiltrate the spinal cord parenchyma, which may contribute to the development of an intramedullary myelographic pattern.

It is important to realize that both meningiomas and MNSTs tend to be associated with an intradural extramedullary pattern. Also, both tumors appear to have a predilection for the cervical spinal cord. In some cases of MNST, an enlarged intervertebral foramen evident on radiographs, CT or MRI, and/or an enlarged nerve root identifiable with CT or MRI, may help in distinguishing a tumor as being a MNST, rather than meningioma. The absence of such distinguishing imaging results, however, does not rule out the possibility of MNST. Definitive diagnosis of spinal tumors in all cases requires histopathologic evaluation of affected tissue. This is usually not feasi-

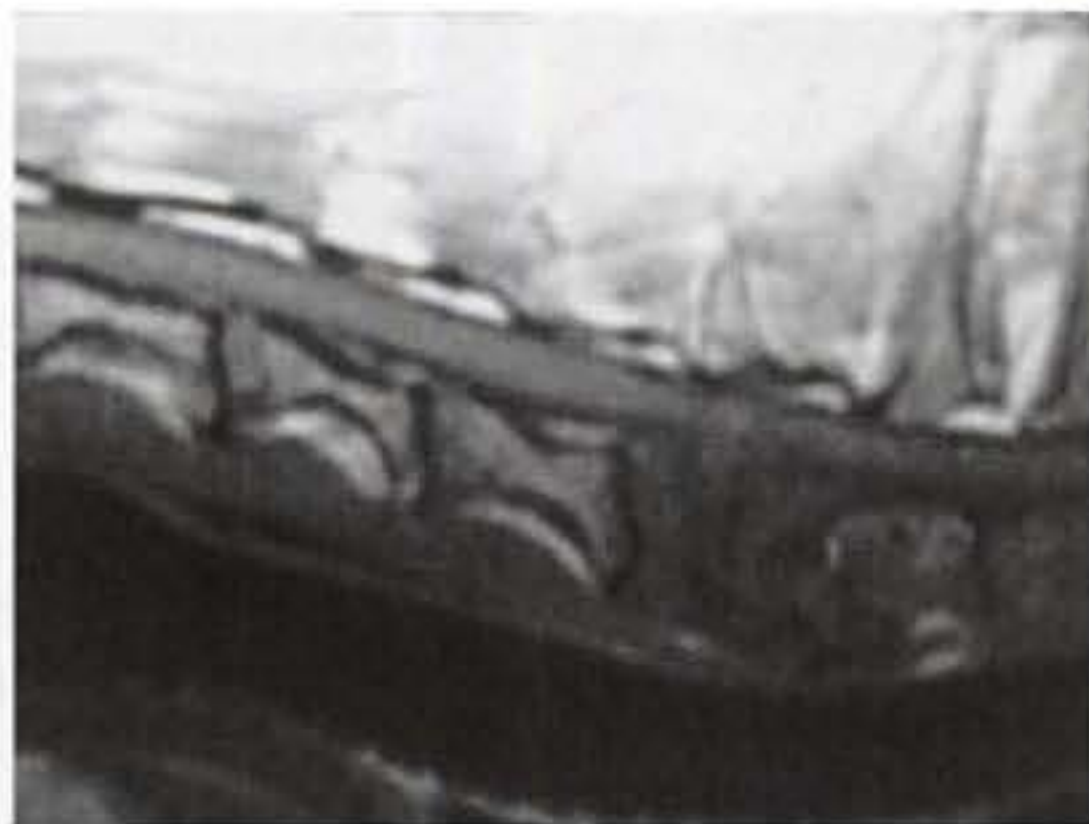


Fig. 9.24. Sagittal T1-weighted image of a dog's cervical spine, demonstrating a bony tumor of the C7 vertebra.



Fig. 9.25. Transaxial T2-weighted image of a dog's cervical spine, demonstrating a large soft-tissue mass invading the vertebral canal. A malignant nerve sheath tumor was suspected.

ble without surgical intervention. However, fluoroscopic or CT-guided needle biopsy may provide a diagnosis in some cases.

4. As with brain tumors, therapy for dogs and cats with spinal tumors can be divided into supportive and definitive treatments. Supportive therapies are directed against secondary sequelae of the spinal tumor (e.g., cord edema, pain), whereas definitive therapies are aimed at elimination of neoplastic tissue. Supportive therapy consists of anti-inflammatory doses of glucocorticoids (e.g., prednisone, 0.5 mg/kg, PO, q 12 hr), which can be increased or decreased as needed, with or without additional pain-relieving drugs (e.g., narcotics). Definitive therapy consists primarily of surgery and megavoltage radiation therapy, similar to brain tumor definitive therapy (see Chapter 4). Chemotherapy is indicated for lymphosarcoma and myeloma. There are no reports describing the use of chemotherapy for other spinal neoplasms (e.g., gliomas) in dogs and cats.

The prognosis for dogs and cats with spinal neoplasia treated with supportive therapy alone is poor. Although data are lacking, these patients will likely be euthanized because of progressive spinal cord dysfunction within several weeks to several months, depending on the tumor type. For most canine and feline spinal tumors, there is a lack of meaningful prognostic information based upon large numbers of cases in which definitive therapy was pursued. With the exception of lymphosarcoma, there is a notable absence of prognostic information pertaining to feline spinal neoplasia. In a recent report, prognostic data concerning nonlymphoid spinal neoplasia in eleven cats were described. Several of the cats experienced prolonged remissions following surgical intervention,

- b. Clinical signs of neck pain and rigidity, lameness, and reluctance to move are common. The cervical vertebral exostoses can compress spinal nerves, leading to hyperesthesia.
- c. Changing the diet may halt further progression of the disease, but the prognosis for recovery is poor.
- 2. Methionine deficiency-related spinal myelinopathy^{1,76,186,187}
 - a. A unique myelopathy has been described in hunting dogs in Europe. English Foxhounds, Harriers, and Beagles have been reported to develop a diffuse myelopathy that is associated with being fed a diet composed primarily or exclusively of ruminant (cow and sheep) stomachs for at least six months. The predominant lesion is spinal cord demyelination, with relatively mild axonal damage. Affected dogs have significantly lower serum methionine levels and significantly higher liver methionine synthetase activity, in comparison with age-matched controls fed a balanced diet. The dietary-induced methionine deficiency is believed to cause a disruption of spinal cord myelin integrity.
 - b. Adult hunting dogs between 2 and 7 yr of age have been described with this disorder. A gradual onset of mild paraparesis and pelvic limb ataxia is typical, and the gait often worsens with exercise. There is often exaggerated flexion of the pelvic limbs during ambulation. Another characteristic feature of this disorder is a loss of panniculus (cutaneous trunci) reflex caudal to the thoracolumbar junction area of the spine.
 - c. Diagnosis of this condition is based primarily upon dietary history combined with characteristic clinical signs of a progressive T3–L3 myelopathy. Bloodwork and urinalysis results are within normal limits, as are results of CSF analysis and myelography. Serum methionine levels are abnormally low and liver methionine synthetase levels are abnormally elevated. In dogs that were euthanized for this condition, histopathologic evidence of demyelination with minor axonal damage is appreciated throughout white matter of the spinal cord as well as some brain-stem areas.
 - d. Treatment of the condition is switching affected dogs to a balanced diet. The prognosis for full recovery is favorable after institution of sound feeding practices.

E. Inflammatory/infectious

1. Diskospondylitis^{1,188}

This is an infection of the intervertebral disk and surrounding vertebral endplates that is usually caused by bacteria. The most common bacteria incriminated are *Staphylococcus* species. Other bacteria and fungal organisms have also been incriminated. A pathologically similar, but radiographically distinct disorder, called vertebral physitis, has also been described. Any vertebral level can be affected, but the L7–S1 space is one of the most common. This disease will be discussed in more detail in Chapter 10.

2. Meningitis/meningomyelitis^{1,189–201}

levels is a characteristic CSF finding. While some dogs respond temporarily to antibiotic therapy, the prognosis is poor.

- (4) Aseptic meningitis/polyarthrititis of Akita dogs—Two of eight young (less than 8 mo old) Akita dogs with a syndrome similar to juvenile rheumatoid arthritis of people had evidence of aseptic meningitis. One pup responded poorly to immunosuppressive therapy and one pup was euthanized (no therapy attempted).
- (5) Feline polioencephalomyelitis—This is an uncommon subacute to chronic disorder of both young and adult cats. A nonsuppurative inflammatory process of unknown etiology (viral suspected) leads to neuronal, axonal, and myelin loss in both the brain and spinal cord. Clinical signs of myelopathy (ataxia and paresis of pelvic limbs or all four limbs) predominate, but intention tremors and focal seizure activity may be observed. Leukopenia may be demonstrated by a CBC. Antemortem diagnosis is difficult and the prognosis is poor.
- b. Infectious causes (see also Chapter 4)—Appropriate references dealing with diagnosing and treating infectious diseases should be consulted for more detail. All of the following infectious diseases may result in clinical signs of myelopathy, with or without signs suggesting brain dysfunction:
 - (1) Viruses, such as canine distemper virus, feline coronavirus (FIP).
 - (2) Bacteria, such as *Staphylococcus* species, *Streptococcus* species, coliforms. An apparently rare disease syndrome called spinal epidural empyema has recently been reported to cause a severe myelopathy in dogs. Three dogs have been described with myelographic evidence of extensive purulent epidural fluid accumulation over several vertebral lengths. The hallmarks of this disorder are spinal hyperesthesia and fever. There may or may not be radiographic evidence of vertebral osteomyelitis. The key to successful management of this rare disorder appears to be rapid diagnosis and aggressive medical and surgical treatment.
 - (3) Fungi, such as cryptococcus, coccidioidomycosis.
 - (4) Rickettsiae, such as *Ehrlichia*, *Rickettsia*, Rocky Mountain spotted fever.
 - (5) Protozoa, such as toxoplasma, neospora.
 - (6) Parasitic, such as dirofilaria, cuterebra.
 - (7) Algae, such as prototheca.

F. Ischemic/vascular

1. Fibrocartilaginous embolic myelopathy (FCE)^{1,76,77,202–207}

- a. This is a common syndrome caused by the embolization of arterial and/or venous supply to an area of the spinal cord. The embolizing material has been identified as fibrocartilage and is believed to originate from the nucleus pulposus of the intervertebral disk. The mechanism or mechanisms by which this material reaches the spinal cord vasculature from the disk is/are unknown. Theories center either around venous entry of disk

material (e.g., extrusion either directly into a venous sinus or venous system of vertebral bone marrow—a Schmorl's node) with retrograde movement into the spinal arterial system, or direct entry to the spinal cord arterial system (e.g., into normal surrounding vasculature or neovascularization over the annulus fibrosus associated with concomitant Type II disk degeneration).

- b. This disease usually affects nonchondrodystrophic dogs, principally of large and giant breeds, but smaller nonchondrodystrophic dogs (e.g., Shetland sheepdogs, miniature Schnauzers) and, rarely, cats have been afflicted. Approximately 20% of FCE patients are dogs less than 20 kg. A recent study revealed that FCE is the most common cause of myelopathy in miniature Schnauzers. Age of onset of clinical signs ranges from the juvenile to the elderly, but most are young to middle-aged (1- to 7-yr-old) adults. The FCE patient typically presents with a history of peracute to acute onset and progression of clinical signs. Most dogs will reach peak severity of neurologic dysfunction within 24 hr, many within 6 hr or less. Rarely, dogs with FCE may develop dysfunction over several days. Owners often observe the affected dog to cry out in apparent pain during exercise or a mild traumatic event, shortly before the onset of neurologic dysfunction. These dogs are often not in any detectable pain by the time they are presented to the clinician. In one study, it was found that spinal hyperesthesia could be elicited in 21% of dogs with FCE. It is the author's experience that spinal hyperesthesia can often be elicited in FCE patients that are examined soon after the onset of neurologic dysfunction. Clinical signs of myelopathy will vary, depending upon both the location and severity of the spinal cord ischemic injury. Deficits are often asymmetric with FCE and the clinical signs of dysfunction are not progressive.
- c. Diagnosis of FCE is based upon history, signalment, clinical signs, and ruling out other causes of acute myelopathy. Results of plain radiography, CSF evaluation and myelography are typically normal. Myelographic evidence of spinal cord swelling (intramedullary pattern), and nonspecific CSF abnormalities (e.g., elevated protein level, mild pleocytosis, xanthochromia) may be seen in some cases. The author has recently imaged several suspected FCE patients with MRI; hyperintense parenchymal lesions (suspected to be edematous, infarcted tissue) on T2-weighted images are characteristic.
- d. Treatment usually consists of early glucocorticoid administration (see Spinal Trauma in this chapter) and physical therapy, the latter of which may be protracted. The prognosis for functional recovery is extremely variable, reflecting the variability in lesion severity characteristic of this disease. The prognosis is good for dogs that regain functional status within the first 2 wk of spinal cord injury. For nonambulatory dogs, especially of the large and giant breeds, the prognosis for recovery is guarded. Negative prognostic indicators appear to include loss of pain perception

(nociception), severe LMN damage, and owner reluctance to pursue prolonged physical therapy. The degree of owner reluctance is often associated with the size of the dog (e.g., prolonged physical therapy and bladder management for a paralyzed Great Dane may not be feasible for many owners). The mortality rate for large- and giant-breed dogs with FCE has been reported as 64%, and is most likely linked to the difficulty in providing long-term physical therapy in these breeds during neurologic recovery. In the recent report on miniature Schnauzers, only 22% of the cases were euthanized. While many of the surviving dogs regained functional status, most retained some neurologic deficits.

2. Traumatic feline ischemic myelopathy⁷⁶

A syndrome of acute pelvic limb paralysis from ischemic myelopathy, associated with evidence of abdominal injury, has been described in cats. The ischemic cord damage is thought to be due to vasospasm and/or thrombosis of lumbar arteries that supply spinal branches to the cord. The proposed cause is compressive injury to the abdomen from an automobile tire. Treatment of this disorder has not been reported.

G. Toxic

Both strychnine and the exotoxin tetanospasmin from *Clostridium tetani* act at the spinal cord level to produce clinical signs of muscle rigidity. These similar disorders will be discussed in Chapter 13, since they present clinically as disorders of muscle tone.

H. Traumatic^{1,208–221}

Acute spinal cord trauma can occur from a number of causes, including acute disk extrusions, FCE, and external forces (e.g., hit by automobile). Injury from external forces can occur with or without evidence of attendant vertebral instability. The pathophysiological events associated with acute spinal trauma are similar to those associated with head trauma (Chapter 5). Similar to head trauma, the goal of therapy is to attenuate the secondary autolytic processes set in motion by the primary insult. Prevention of further primary cord damage by surgical decompression and/or stabilization (e.g., progressive disk extrusion, vertebral fractures, subluxations, and luxations) may also be indicated. Specific diagnostic tests usually involve plain radiographs of the spine with or without myelography. In general, there are two major categories of therapy for spinal cord trauma:

1. Medical therapy

- a. In the case of external trauma, such as automobile-associated injury, the patient must first be evaluated according to the ABCs of trauma management, and life-threatening injuries must be addressed before evaluating the patient's neurologic status. It is important to keep the patient as immobilized as possible when instability of the spine is suspected. Regardless of the etiology of acute spinal trauma, glucocorticoids are often recommended. The only protocol clinically shown to have a positive

influence on outcome is the high-dose methylprednisolone sodium succinate (MPSS) protocol (see Chapter 5). However, the efficacy of this treatment is debatable. It is important to administer MPSS as soon after trauma as is possible. In human spinal trauma (external causes), administering the high-dose methylprednisolone protocol 8 hr or more after trauma is ineffective.

Experimental therapies that have shown some promise for acute spinal cord injury include oscillating field stimulation and local application of polyethylene glycol. Oscillating field stimulation involves application of a weak electrical field of oscillating polarity to the damaged spinal cord region; this treatment is thought to promote neuronal and axonal repair processes. Polyethylene glycol may help reconnect damaged cellular membranes. Mannitol has not exhibited the efficacy in reducing cord edema that has been observed with its use in reducing brain edema.

- b. When instability of the spinal column is confirmed, nonsurgical management may be successful in selected cases. Such management usually consists of prolonged cage confinement with or without external splintage of the spine, with appropriate physical therapy and bladder management. One should not rely too heavily upon external splintage; extreme care in moving these patients must still be exercised. The owner should be informed of the risk of acute worsening of neurologic signs (i.e., if the fracture/luxation displaces) as well as the prolonged recovery time typical of nonsurgically managed spinal instability patients.
 - c. Prognosis is variable and depends upon a number of factors, including neurologic status and ability/willingness of the owner to commit to prolonged care of a nonambulatory pet. In general, there is at least a fair chance of neurologic recovery in patients with intact nociception.
2. Surgical therapy
- a. The guidelines for surgical decision making in cases of Type I disk disease have been discussed. In cases of external spinal trauma with suspected or known instability, there are no definitive rules dictating which patients should have surgery. In general, surgical stabilization and/or decompression is recommended for the following:
 - (1) Moderately to severely displaced vertebral fracture/luxations.
 - (2) Patients with severe neurologic dysfunction (nonambulatory paresis, plegia), especially with diminished nociception caudal to the lesion.
 - (3) Deteriorating neurologic status.
 - (4) Evidence of spinal cord compression on a myelogram (hemorrhage, traumatic disk extrusion, etc.).
 - b. Methods of surgical decompression were discussed under degenerative disk disease. There are numerous methods of vertebral stabilization, including spinous process plating, vertebral body plating, pins and/or screws and methacrylate, and spinal stapling. The method(s) chosen depends upon patient size, lesion location, and surgeon preference.

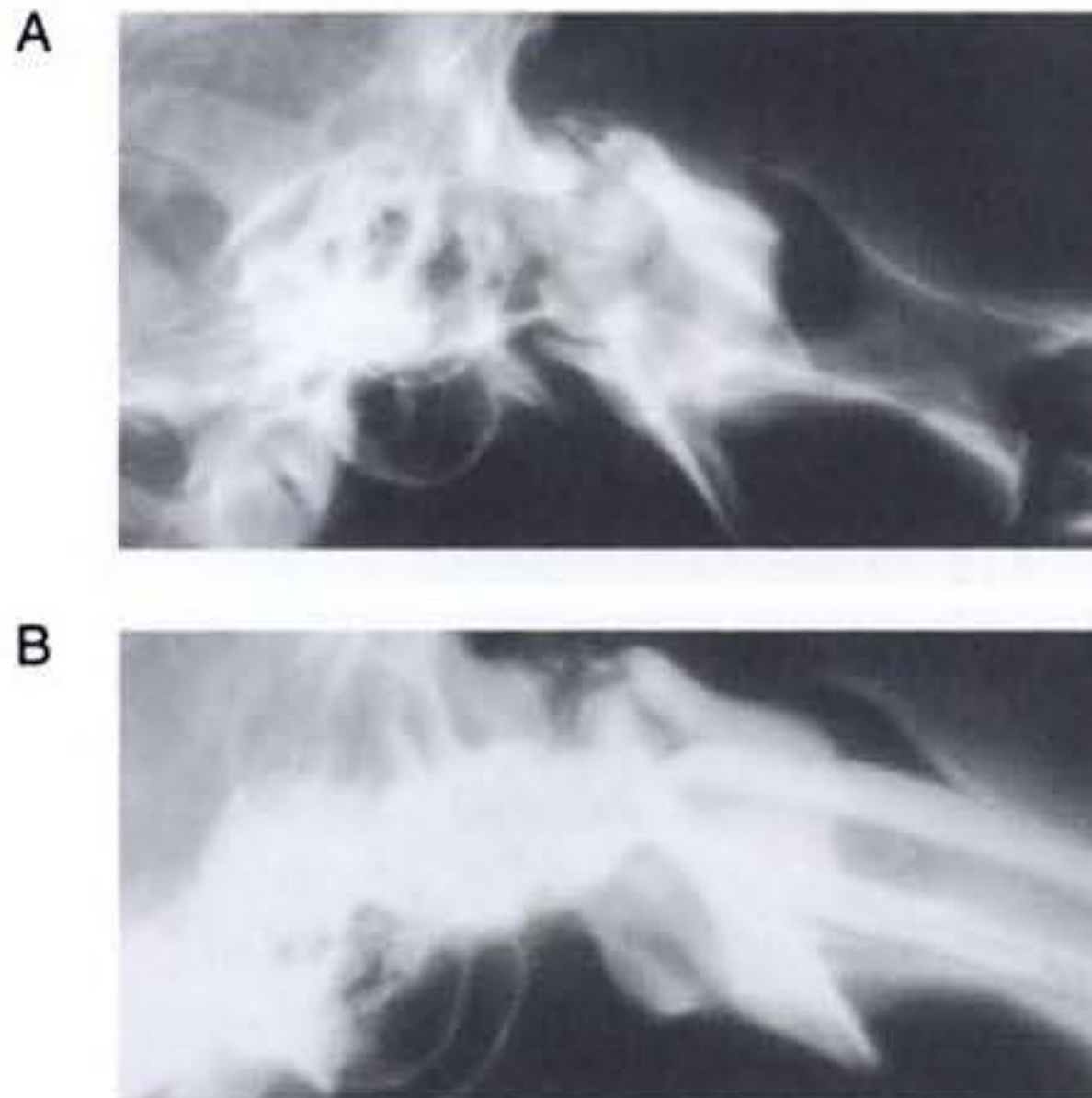


Fig. 9.26. Lateral premyelographic (A) and postmyelographic (B) images of a dog's cervical spine, demonstrating a dorsal compressive tumoral calcinosis lesion between the occiput and C1 vertebra (From: Dewey CW, Coates JR, Miscellaneous spinal disorders, in Slatter D (ed), *Textbook of Small Animal Surgery*, 3d ed. Philadelphia, WB Saunders Co, 2002. Reprinted with permission).

appears more prominently as an animal ages. The margins of the exostoses are usually smooth. Spondylosis is often associated with Type II disk protrusions, especially at the lumbosacral junction, but by itself is not an important clinical entity. This syndrome must be distinguished from diskospondylitis (Chapter 10).

4. Disseminated idiopathic skeletal hyperostosis (DISH)^{226,227}

This idiopathic disorder refers to extensive periarticular calcification and ossification throughout the body, including the vertebrae. It is thought that, for some unknown reason, DISH patients have an exaggerated bony proliferative response to minor bone stresses. DISH has been described in two dogs, a 4-yr-old male Labrador retriever, and a 4-yr-old female Great Dane. The radiographic lesions were similar to those reported in people with the same disorder. The characteristic radiographic appearance of vertebrae in patients with DISH is "flowing" ossification primarily at the ventrolateral aspect of the spine, extending for at least four contiguous vertebrae (Fig. 9.27). There may also be ossification of the interspinous ligaments dorsally. Ossification at areas of ligamentous attachments (enthesiophytes) is also characteristic. Despite the extensive periarticular formation of new bone, the joints themselves are normal (i.e., no degenerative joint disease). Clinical signs of gait abnormalities and decreased joint mobility reflect the restrictive effects of the



Fig. 9.27. Lateral thoracolumbar radiograph demonstrating DISH in a dog

periarticular bone formation. There is no known effective treatment for this enigmatic disorder.

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the pelvic limbs. This can be as mild as delayed proprioceptive positioning reactions or as severe as pelvic limb ataxia with dragging the dorsal aspect of the toes ("knuckling"). The deficits may or may not be symmetric.

- C. Voluntary motor deficits—motor deficits to the muscles innervated by the sciatic nerve and caudal (coccygeal–tail innervation) nerves may be clinically detectable, as the cord segments and nerve roots of the cauda equina give rise to these nerves. Pelvic limb weakness may be apparent with damage to sciatic nerve contributions, and decreased to absent tail tone and movement may occur with damage to caudal segments and/or nerve roots. In some cases, the patient may be observed to exhibit an abnormally low tail carriage, which is often noticed by the owner.
- D. Abnormal reflex activity—decreased to absent withdrawal and gastrocnemius reflexes may be appreciated. The patellar reflex is typically normal or may appear hyperreflexive. Caudal thigh muscles normally inhibit the action of the quadriceps muscle group when the patellar reflex is elicited. Removal of this tonic antagonistic influence by disrupting the nerve supply to the caudal thigh muscles may result in an apparently hyperactive patellar reflex (i.e., patellar pseudo-hyperreflexia). A decreased to absent perineal reflex may result from cauda equina lesions.
- E. Urinary and fecal abnormalities—varying degrees of urinary and fecal incontinence may occur with damage to sacral segments and/or roots. Bladder dysfunction is classically LMN in nature (see Chapter 11).
- F. Nociceptive (pain perception) deficits in areas of the pelvic limbs (see Chapter 12 for autonomous zones), perineum, and tail may occur with severe lesions of the cauda equina.

II. Disorders Affecting the Cauda Equina in Dogs and Cats (see Table 10.1)

A. Degenerative

1. Degenerative lumbosacral stenosis^{1–33}

- a. This is a common disease syndrome that typically affects adult (usually middle-aged to older), large-breed dogs. According to some reports, there is a male predilection for this disease. The German Shepherd dog appears to be particularly predisposed to degenerative lumbosacral stenosis. The pathogenesis involves Type II degeneration and subsequent protrusion of the L7-S1 intervertebral disk into the vertebral canal (Fig. 10.1). There are often other degenerative changes at the lumbosacral junction, indicative of chronic instability at this articulation. Ventral spondylosis is often appreciated at the lumbosacral junction in these patients, but by itself, this radiographic finding has little clinical significance. Some of the degenerative

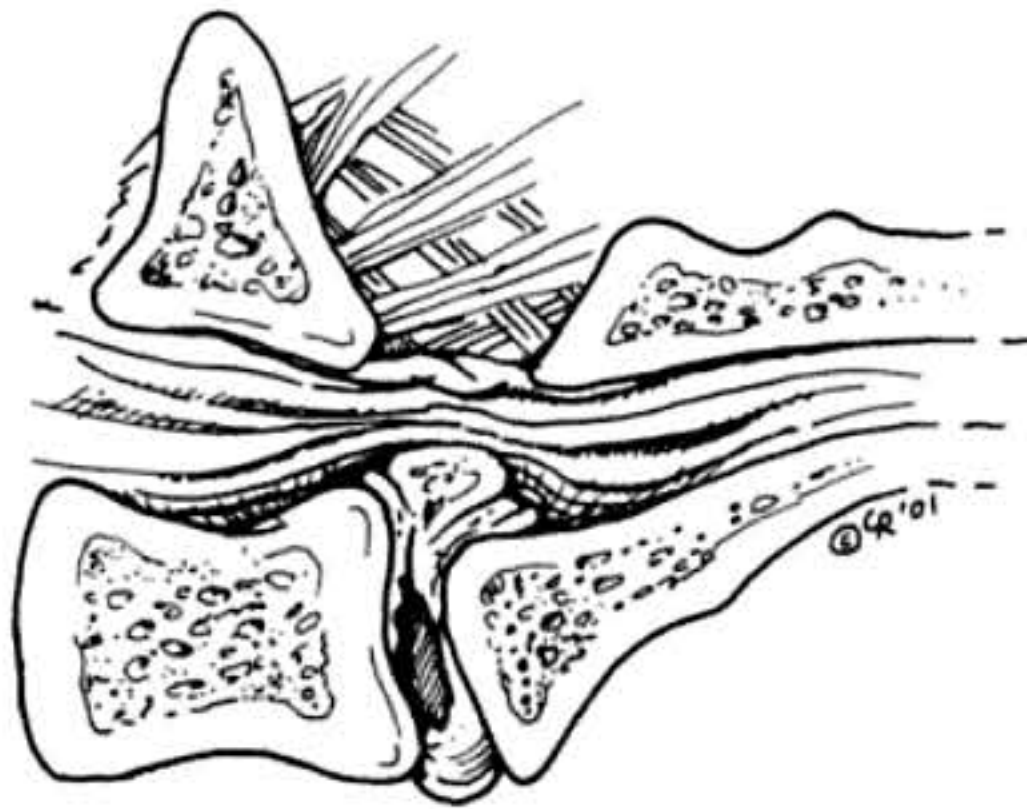


Fig. 10.1. Schematic illustration depicting a protruding disk at the L7–S1 intervertebral disk space (Illustration by Carol Rudowsky).

changes, other than disk protrusion, that may lead to compression of the cauda equina include:

- (1) Collapse of the intervertebral disk space at L7–S1 and subluxation of the L7–S1 articular facets. The craniodorsal aspect of the sacrum may become displaced ventral to the caudodorsal aspect of the L7 vertebra.
- (2) Hypertrophy and folding inward (ventrally) of the interarcuate ligament (ligamentum flavum) located between the dorsal laminae of L7 and S1.
- (3) Hypertrophy of soft tissue structures (e.g., joint capsule) as well as osteophyte formation associated with the L7–S1 articular facets.

Reasons for this chronic degenerative process are unknown. In German Shepherd dogs, the presence of transitional vertebrae at the lumbosacral junction has been associated with development of degenerative lumbosacral stenosis.

- b. Clinical signs are variable, but lumbosacral pain is an early and consistent finding. Pain may be manifested in a number of ways, such as reluctance to rise or sit, and unilateral or bilateral pelvic limb lameness. Pain and lameness may be acute or chronic and may be persistent or episodic. These clinical signs may be misinterpreted as being due to orthopedic disease, most notably hip dysplasia. Many of these dogs have radiographic evidence of hip dysplasia, making this a particularly easy trap to fall into when the only obvious clinical sign of an abnormality is pain and/or pelvic limb lameness. If untreated, clinical signs of dysfunction may progress to proprioceptive loss in the pelvic limbs, voluntary motor weakness (in the distribution area of the sciatic nerve), and urinary/fecal incontinence, usually in that order. In the author's experience, deficient pelvic limb withdrawal reflexes are most apparent at the hock level in cases of degenerative lumbosacral stenosis; flexion at the hip and stifle regions

often appears normal. Although typically indicative of progressively severe cauda equina compression, urinary and/or fecal incontinence occasionally comprise the initial primary clinical complaint in cases of degenerative lumbosacral stenosis. Careful palpation of the lumbosacral area, including lordosing the caudal spine while pressing on the lumbosacral area, will usually elicit a pain response in affected patients (Fig. 10.2). Most dogs afflicted with this disease also have obvious deficits on proprioceptive positioning tests of the pelvic limbs.

- c. Diagnosis of degenerative lumbosacral stenosis is based upon signalment, historical and clinical findings, and results of diagnostic imaging of the lumbosacral region. The definitive diagnosis of degenerative lumbosacral stenosis is made by imaging of the lumbosacral area and demonstrating compression of the cauda equina. Although degenerative changes at the lumbosacral junction (e.g., spondylosis, malalignment of the sacrum with the L7 vertebra) may often be appreciated on plain radiographs of the region, additional imaging is necessary to demonstrate cauda equina



Fig. 10.2. Lordosing the lumbosacral spine while applying dorsal pressure often elicits a painful response in dogs with degenerative lumbosacral stenosis.

compression. A number of procedures have been advocated, including myelography, epidurography, vertebral sinus venography, diskography, computed tomography (CT), and magnetic resonance imaging (MRI). Since the terminal thecal sac (subarachnoid space) of the spinal cord in large-breed dogs often ends cranial to the lumbosacral junction, myelography (Fig. 10.3) may not consistently provide useful information. Vertebral sinus venography is considered to be both a technically difficult and unreliable imaging procedure. Diskography (Fig. 10.4) is an accurate imaging method for degenerative lumbosacral stenosis but provides information primarily limited to the intervertebral disk. Epidurography is also considered to be a relatively accurate contrast procedure to identify cauda equina compression. Combination diskography/epidurography (Fig. 10.5) has also been demonstrated to be a useful diagnostic imaging method for degenerative lumbosacral stenosis. In the author's experience, CT (Fig. 10.6) and MRI (Fig. 10.7) provide the most detailed structural information regarding the cauda equina, including information concerning the L7–S1 intervertebral foramina and L7 nerve roots. Concurrent EMG performed on the epaxial, tail, and pelvic limb musculature may improve the accuracy of diagnosis with the various imaging modalities.

- d. Treatment of the patient with degenerative lumbosacral stenosis may be nonsurgical or surgical, similar to other disk-associated diseases. Treatment



Fig. 10.3. Lateral myelographic view of a cat's lumbosacral region. Since the spinal cord usually ends at the S1 level in cats, a mildly protruded L7–S1 intervertebral disk is evident on this image.



Fig. 10.4. Lateral spinal radiographic image of a dog with degenerative lumbosacral stenosis. A myelogram failed to outline the lumbosacral region, so a diskogram was subsequently performed. A protruded L7–S1 intervertebral disk is evident on diskography.



Fig. 10.5. Combination diskography/epidurography (lateral view) in a dog with degenerative lumbosacral stenosis (From Sharp NJH, Wheeler SJ (eds), *Small Animal Spinal Disorders-Diagnosis and Surgery*, 2d ed. New York, Elsevier Publishing, 2003. Reprinted with permission).

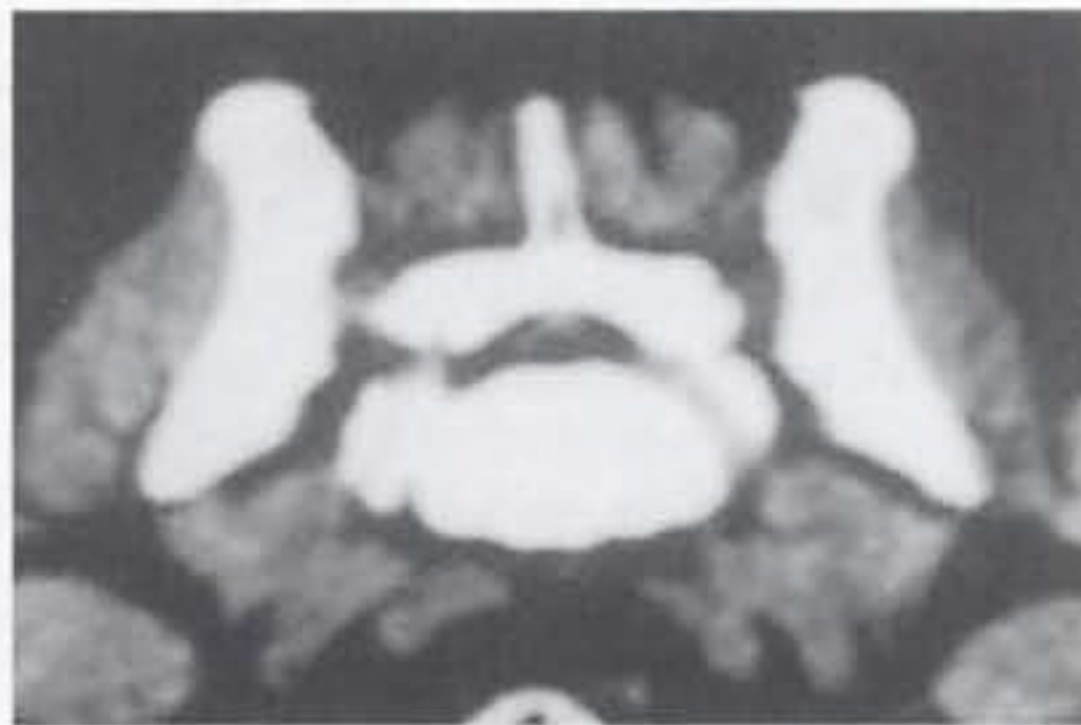


Fig. 10.6. Transaxial CT image of the lumbar region of a dog. Bilateral L7-S1 foraminal narrowing is evident.



Fig. 10.7. Sagittal MR image (T2-weighted) of a dog, exhibiting a large disk protrusion at the L7-S1 intervertebral disk space.

decisions are based primarily on severity of clinical signs; there appears to be no clear correlation between extent of cauda equina compression evident on imaging and disease severity or postoperative outcome. Nonsurgical therapy consists of enforced rest and anti-inflammatory medication (either nonsteroidal drugs or prednisone, *not both*), and is often recommended for dogs with signs of hyperesthesia only. Nonsurgical therapy tends to be either transiently effective or ineffective for this disease.

In patients with neurologic deficits, or patients in which pain is refractory to nonsurgical management, surgery is chosen as the preferred mode of therapy. Surgery usually consists of a dorsal laminectomy over the L7–S1 interspace (Fig. 10.8), often combined with removal of hypertrophied soft tissue (e.g., annular disk material). Enlargement of the L7–S1 intervertebral foramen (foraminotomy) or removal of the articular facets (facetectomy) may also be required if compression of the L7 nerve root is appreciated. Most surgeons do not advocate surgical stabilization of the lumbosacral joint but this may be advisable in some cases (e.g., bilateral facetectomy). The prognosis for functional recovery from this disorder is generally good to excellent with surgical intervention. Successful outcomes after surgery have been reported in 78% to 94% of cases. It appears that, although improvement in continence may occur in dogs with presurgical fecal and/or urinary incontinence (over weeks to months following surgery), resolution of incontinence is not likely to occur in most cases. Incontinence failed to resolve after decompressive surgery in 55% to 87% of reported cases. In a recent study, presurgical incontinence was the only clinical feature correlated with a poor postoperative outcome. Improvement or resolution of incontinence was found to be much less likely in dogs that had been incontinent for more than one month, compared to those that had shorter histories of incontinence. Reported recurrence rates for degenerative lumbosacral stenosis vary between 3% and 18%. Recurrence is probably more likely in very active dogs (i.e., working dogs).

2. Type I degenerative disk disease

- a. Occasionally, Type I disk extrusions will occur in a caudal lumbar disk, leading to signs of cauda equina dysfunction.
- b. Clinical signs of pain and dysfunction tend to occur acutely, similar to Type I disk extrusions in other spinal locations. Pelvic limb “root signature” (see Chapter 9) may occur with lateralized Type I disk extrusions in the caudal lumbar region.
- c. Specifics regarding diagnosis, treatment, and prognosis of patients with Type I disk disease are discussed in Chapter 9. Diagnostic imaging other than myelography (e.g., diskography, epidurography, CT, MR) may be necessary to demonstrate a Type I disk extrusion of the L7–S1 intervertebral disk.

B. Anomalous/developmental

1. Congenital vertebral malformations^{1,2,4–6,30,34–38}

For the most part, the congenital vertebral malformations discussed in Chapter 9 can occur in the lumbosacral region. Clinical features, diagnostic and treatment options, and prognosis are similar as described for other areas of the spine. There are some vertebral malformations that are specific to the lumbosacral area:

- a. Idiopathic lumbosacral stenosis—this is an ill-defined disorder primarily in adult, small- to medium-sized dogs that is most likely due to abnormal

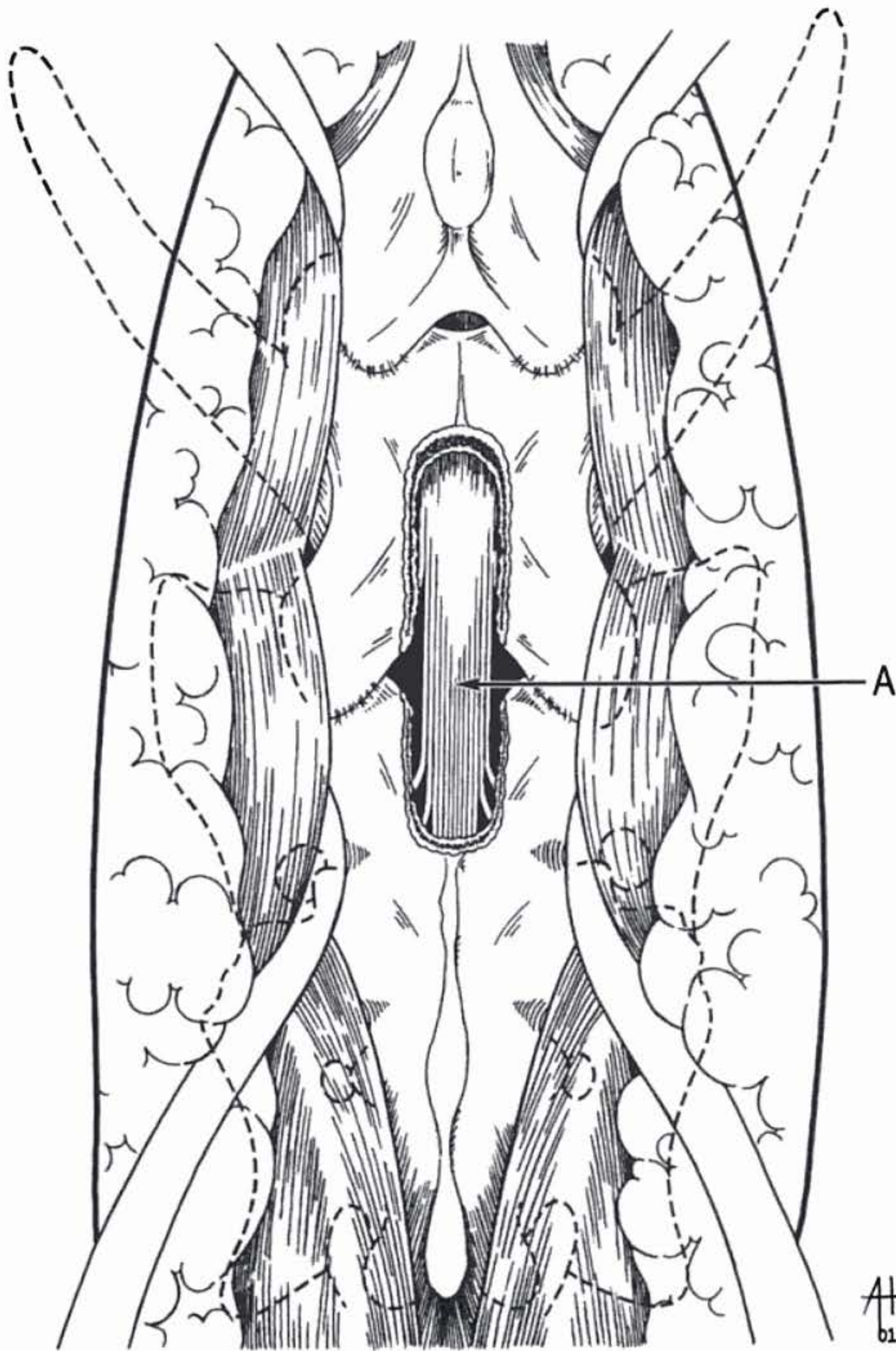


Fig. 10.8. Schematic illustration of a dorsal laminectomy at the L7–S1 region (Illustration by Anton Hoffman, from Coates JR, Hoffman AG, Dewey CW, *Surgical approaches to the spine*, in Slatter D (ed), *Textbook of Small Animal Surgery*, 3d ed. Philadelphia, WB Saunders Co, 2002. Reprinted with permission). A, cauda equina.

a large contributing factor to the clinical dysfunction, there is no effective therapy for this condition. If the defect is open to the environment, the development of life-threatening meningomyelitis is a concern.

- b. Tethered cord syndrome—this refers to a disorder in which caudal traction is placed on the cauda equina due to abnormal fixation of the filum terminale (spinal cord meningeal termination) during embryonic development. Traction causes neurologic dysfunction which can sometimes be alleviated by surgical intervention. Tethered cord syndrome can occur primarily as a defect of the filum terminale, or more commonly as a component of spina bifida and meningocele/myelomeningocele.
4. Hydromyelia and syringomyelia
Hydromyelia and syringomyelia may affect the spinal cord contributions to the cauda equina. Specifics of hydromyelia/syringomyelia are discussed in Chapter 9.
5. Pilonidal sinus (dermoid sinus)
This disorder may occur in the sacrocaudal region of the spine. Pilonidal sinus is discussed in more detail in Chapter 9.

C. Neoplastic

Various primary and secondary bony and soft tissue neoplasms (discussed in Chapter 9) can affect the lumbosacral region and the cauda equina (Fig. 10.10).

D. Infectious/inflammatory

1. Diskospondylitis^{1,4,5,42-59}
 - a. Diskospondylitis refers to an infection of the intervertebral disk and its contiguous vertebrae, usually by coagulase-positive *Staphylococcus* bacteria (e.g., *intermedius*, *aureus*). Other bacterial organisms have been reported



Fig. 10.10. Transaxial MR image (T1-weighted with contrast) of the lumbosacral region of a dog. A large mass invading the vertebral canal is evident. A chondrosarcoma was diagnosed surgically.



Fig. 10.11. Typical radiographic appearance of severe diskospondylitis at the L7–S1 intervertebral disk space (lateral view).

missed if the radiographs are performed in the awake patient. In some cases, bone scintigraphy, computed tomography (CT), or MRI of suspected lesions may be valuable.

Bloodwork results are often normal, although leukocytosis is occasionally revealed by a complete blood count. Urinalysis may reveal evidence of a urinary tract infection in some dogs. Bacteria may be cultured from the blood, urine, and/or affected disk spaces (fluoroscopically guided needle or surgical aspirate) of some patients. The reported success rate of such culture attempts is variable, but in general is about 50%. There is some evidence that needle aspiration of infected disk space(s) is more sensitive than urine or blood culture. CSF examination and contrast radiography (e.g., myelography, epidurography) should be considered in those patients with severe neurologic deficits, especially in nonambulatory patients. The role of contrast radiography in diskospondylitis is controversial. However, compressive lesions that are potentially surgically correctable (e.g., concurrent disk extrusion/protrusion, inflamed or granulomatous epidural fat) may not be appreciated without contrast studies. In a recent study, no adverse effects were associated with myelography or epidurography in dogs with diskospondylitis. Compressive lesions were identified in over half of the dogs in that study, and the vast majority (73%) were soft tissue versus bony lesions. However, the median degree of compression was small (5%), and often was not severe enough to explain the degree of neurologic deficits. Other factors, such as interference to intrinsic spinal cord blood supply by inflammatory mediators and/or dynamic vertebral subluxation, are likely involved in causing neurologic dysfunction in cases of diskospondylitis. Although *Brucella* is an uncommon cause of diskospondylitis, it needs to be ruled out (e.g., rapid slide agglutination test, card test, etc.) due to its zoonotic potential.

- d. Ideally, medical treatment of diskospondylitis is guided by culture and antibiotic sensitivity testing of the offending organism. Since the organism



Fig. 10.12. Lateral postoperative radiographic image of an L7–S1 fracture/luxation repaired with pins and PMMA.

region. However, there are some aspects specific to the cauda equina region to be considered. In contrast to the spinal cord segments, nerve roots of the cauda equina may experience considerable stretching with displaced fractures of the lumbosacral area, yet still remain structurally and functionally intact. Surgical repair of caudal lumbar and lumbosacral fracture/luxations (Fig. 10.12) is often challenging, due to the sparse amount of bone available caudal to the injury for placing implants (e.g., pins, screws).

Cats will occasionally present with fracture/luxations of the sacrococcygeal region, due to suspected traction injury. It is theorized that the tails of these cats are trapped by car tires as the cats are running to avoid being hit. The resultant traction applied to the cauda equina may result in temporary or permanent neurologic damage. These cats often display varying degrees of urinary and fecal incontinence, in addition to tail dysfunction. Some cats also exhibit pelvic limb dysfunction. It is unclear whether or not surgical intervention is of value for this condition. Many of these cats will make full recoveries, especially if anal tone and perineal sensation are intact, and appropriate bladder management is instituted soon after injury. Failure to regain urinary continence within one month of trauma is a negative prognostic indicator.

Sacral fractures often accompany multiple pelvic fractures in dogs and cats. In general, the preservation of pain sensation (nociception) in the areas of innervation of the cauda equina nerve roots is a favorable prognostic indicator. Lateralized sacral fractures in dogs tend to have a better prognosis for neurologic recovery than those located in a more central location.

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Chapter 11

NEUROLOGY AND NEUROPHARMACOLOGY OF NORMAL AND ABNORMAL URINATION

Curtis W. Dewey

I. Introduction^{1,2}

Disorders of urination are commonly encountered in patients with neurologic disease. If not properly managed, they can become more of a health concern than the underlying neurologic disorder. Serious urinary tract problems (e.g., atonic bladder, pyelonephritis) that are secondary to neurologic disease are usually preventable. The key to prevention is a combination of having a sound knowledge base and being a careful examiner. It should never be assumed that a paralyzed dog or cat is urinating adequately because someone saw a pool of urine in that patient's cage. This should *always* be verified (e.g., palpate the bladder, observe for voluntary urination). It is essential that the clinician understand how to deal with what is commonly referred to as the "neurologic bladder." The techniques of bladder expression and urethral catheterization are discussed in Chapter 15. This chapter focuses on the functional neuroanatomy and neuropharmacology of urination. The basic principles outlined in this chapter are necessary for the clinician to understand what type of bladder dysfunction is present (e.g., upper motor neuron [UMN] or lower motor neuron [LMN] bladder) and what drugs are likely to help in managing the dysfunction.

II. Functional Neuroanatomy of the Urinary Bladder and Urethra (see Fig. 11.1)¹⁻¹¹

A. The urinary bladder

1. The urinary bladder is a hollow organ primarily composed of three layers of smooth muscle, collectively termed the detrusor muscle. There are also mucosal, submucosal, and serosal layers. The detrusor muscle contains both adrenergic and cholinergic (muscarinic) receptors that are important in bladder filling and contraction, respectively. The important receptors for efferent autonomic innervation of the body of the bladder are summarized below:
 - a. Beta adrenergic receptors—these sympathetic receptors are innervated by the hypogastric nerve, which in turn originates from the L1–L4 spinal cord segments in the dog (L2–L5 segments in the cat). Stimulation of these receptors causes detrusor muscle relaxation, which allows bladder filling.
 - b. Muscarinic cholinergic receptors—these parasympathetic receptors are innervated by the pelvic nerve, which originates from the sacral (S1–S3) spinal cord segments. Stimulation of these receptors causes detrusor muscle contraction, which leads to bladder emptying.

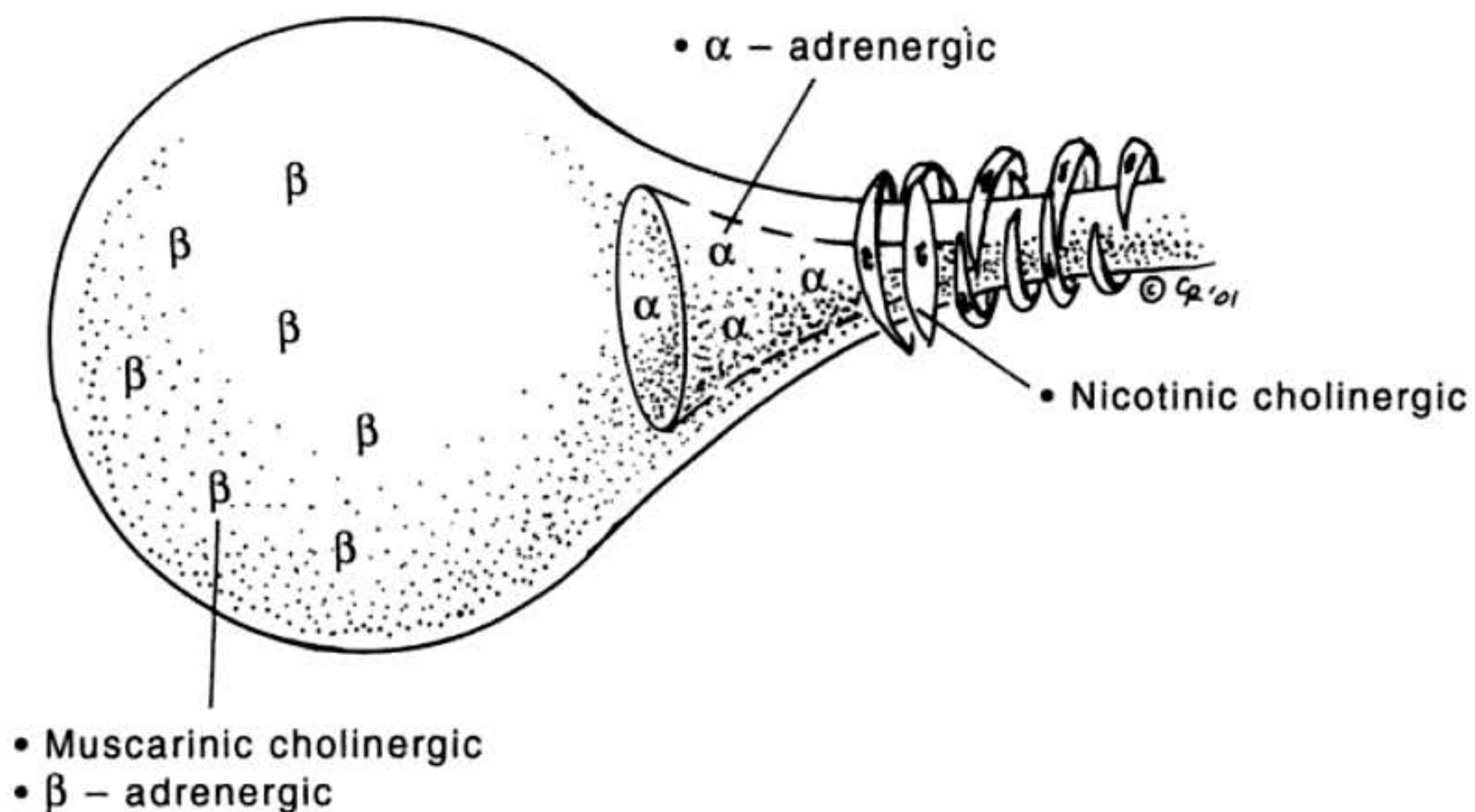


Fig. 11.1. Schematic illustration depicting various receptor types on the bladder wall and urethra (Illustration by Carol Rudowsky).

2. There are also sensory receptors (stretch and pain) in the wall of the bladder. Stretch receptors are innervated by afferent axons that travel through the pelvic nerve toward the sacral spinal cord segments. Pain receptors are innervated by afferent axons that travel in both the pelvic and hypogastric nerves, but primarily in the hypogastric nerves.

B. The urethra

1. For practical purposes, the neck of the bladder can be thought of as the proximal aspect of the urethra. The smooth muscle of the urethra is primarily innervated by the hypogastric nerve and is often considered to represent an internal sphincter, although it is not a true sphincter. The external urethral sphincter is composed of striated muscle that encircles the distal urethra. The external urethral sphincter is innervated by the pudendal nerve. This is a somatic motor nerve whose cell bodies are in the sacral spinal cord segments (primarily S1 and S2). The important receptors for efferent urethral innervation are as follows.
 - a. Alpha adrenergic receptors—these sympathetic receptors are innervated by the hypogastric nerve. Stimulation of these receptors causes contraction of smooth muscle in the neck of the bladder and urethra. This muscle contraction opposes urine flow through the urethra, and therefore facilitates bladder filling.
 - b. Nicotinic cholinergic receptors—these somatic motor receptors are located on the external urethral sphincter and are innervated by the pudendal nerve. The pudendal nerve is under voluntary control, but the

neuronal cell bodies of this nerve within the sacral spinal cord also receive involuntary afferent input. Stimulation of these receptors causes sphincter contraction, which opposes urine flow through the urethra, thus facilitating bladder filling.

2. Similar to the bladder, there are sensory receptors in the wall of the urethra for conveying information concerning distention (stretch), pain, and urine flow. These receptors are innervated by afferent axons that travel in the pudendal nerve toward the sacral spinal cord segments.

III. Local Reflex Arcs^{1,2,5,6-12}

- A. Somewhat analogous to innervation of the limbs, there are inherent spinal reflex arcs involved in bladder filling and emptying. Although there is some level of spinal reflex control of urination in adult dogs and cats, these reflex arcs cease to function autonomously after infancy (3–4 wk in puppies, 7–12 wk in kittens). Thereafter, these reflex centers require descending influences from the brain stem for coordinated urination to occur. The reflex arcs depend on a number of anatomic structures:
 1. The pelvic plexus—this refers to the meshwork of autonomic nerves and ganglia located in the pelvic canal. Within this plexus are afferent and efferent processes of the pelvic and hypogastric nerves.
 2. The pudendal nerve—technically part of the lumbosacral plexus, this nerve is also located in the pelvic canal.
 3. The sacral spinal cord—neuronal cell bodies for the pelvic nerve are located in the intermediolateral gray matter, and neuronal cell bodies for the pudendal nerve are located in the ventral horn gray matter.
 4. The lumbar spinal cord—neuronal cell bodies for the hypogastric nerve are located in the intermediolateral gray matter from L1–L4 spinal cord segments in the dog and L2–L5 segments in the cat.
- B. As the bladder fills, stretch receptors are stimulated and this afferent information is carried via the pelvic nerve to the parasympathetic nuclei in the sacral spinal cord. Efferent impulses from these nuclei through the pelvic nerve initiate detrusor contraction. As the detrusor muscle contracts, another volley of afferent impulses enters the sacral spinal cord. Some of these afferent axons inhibit the sacral neuronal cell bodies of the pudendal nerve, whereas some ascend to the lumbar spinal cord to inhibit the sympathetic cell bodies of the hypogastric nerve. The net result is bladder contraction with nearly simultaneous urethral relaxation and coordinated urination.

IV. The Brain-Stem Micturition Center and the Detrusor Reflex (Fig. 11.2)^{1,2,5-9,11,13-16}

- A. The brain-stem micturition center
Neuronal populations in the brain stem normally coordinate the spinal reflex arcs involved in bladder filling and emptying. These neurons are principally located in

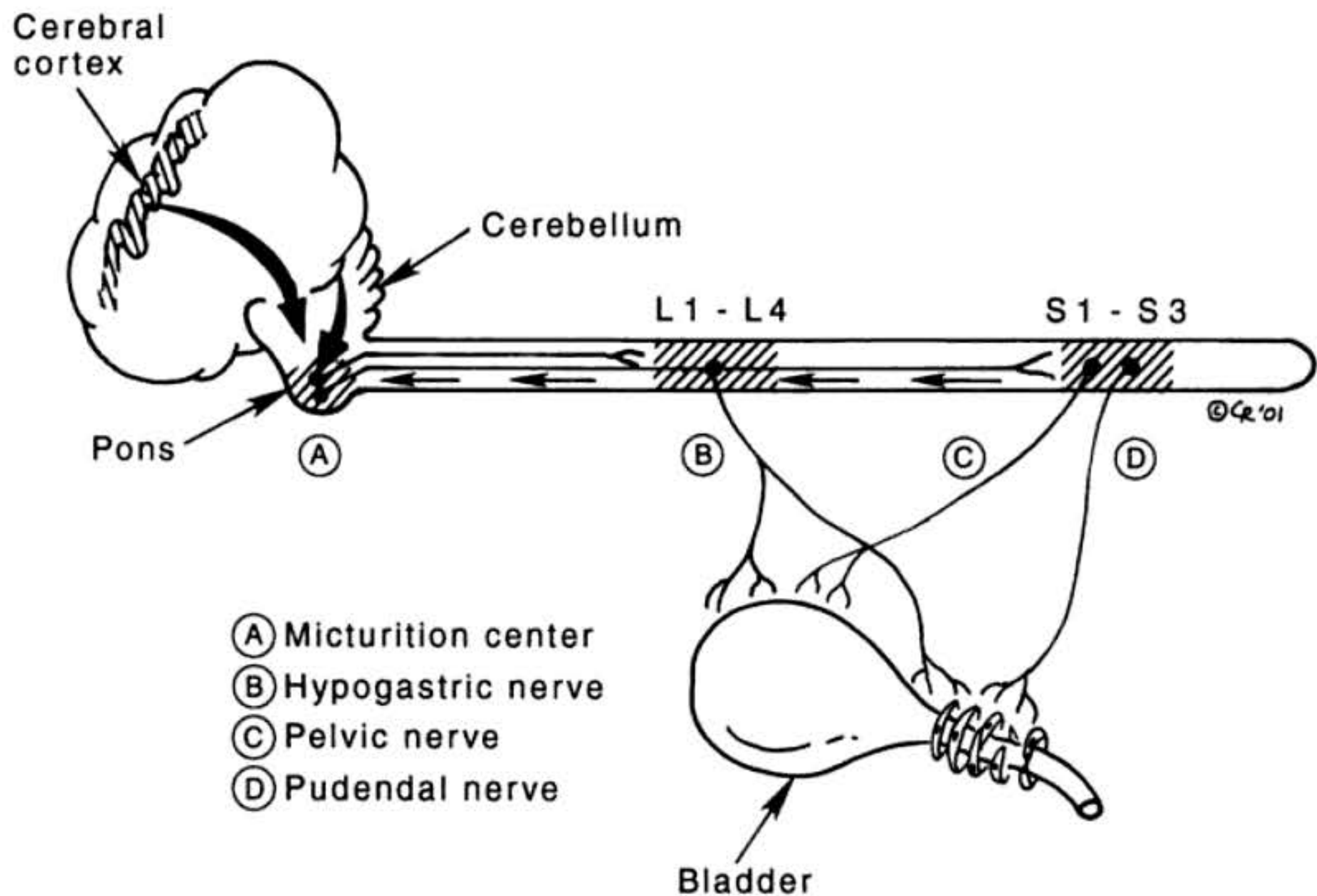


Fig. 11.2. Schematic illustration depicting the neuroanatomy of urination (Illustration by Carol Rudowsky).

the reticular formation of the pons, and to a lesser degree in the midbrain and medulla. Two distinct regions of the pons have been demonstrated to be involved in the filling and evacuation phases of the detrusor reflex, respectively. The dorso-lateral region of the pons contains two groups of neurons involved in the micturition reflex: a medial cell group (M region) and a lateral cell group (L region). Neurons of the M region (Barrington's nucleus) project excitatory axons to the parasympathetic (muscarinic cholinergic) motor neurons in the sacral spinal cord that give rise to the pelvic nerves. Axonal processes from M region neurons also innervate inhibitory interneurons (GABA-ergic) that synapse on nicotinic cholinergic motor neurons in the sacral spinal cord that give rise to the pudendal nerves. Activation of neurons of the M region facilitates urinary bladder evacuation.

Axons projecting from the L region neurons have excitatory synaptic connections with nicotinic cholinergic sacral motor neurons that give rise to the pudendal nerves. Activation of L region neurons facilitates urinary bladder filling. The brain-stem micturition center can be considered the upper motor neuron for normal urination.

B. The detrusor reflex

Some of the afferent impulses (from stretch receptors) from the bladder and urethra are conveyed rostrally up the spinal cord (via spinothalamic pathways) to the brain-stem micturition center, rather than terminating on spinal cord neuronal pools. Neurons of the brain-stem micturition center subsequently convey descending efferent information through the spinal cord (reticulospinal tracts, tectospinal tracts) to the various spinal cord neuronal pools involved in urination. The coordinated act of urination that results from completing this brain-stem/spinal-cord reflex arc is referred to as the detrusor reflex. It should be kept in mind that this is a brain-stem reflex that does not require conscious input (cerebral cortical influence) to operate.

V. Forebrain and Cerebellar Influence on the Detrusor Reflex^{1,2,5-7,11,13-15,17,18}

A. Forebrain influence

Afferent impulses from the bladder reach the cerebral cortex via the pelvic (cat) and hypogastric (dog and cat) nerves and ascending spinal cord tracts. The sensations of stretch and pain are conveyed to the cerebral cortex via these afferent pathways. The detrusor reflex can be consciously inhibited via the cerebral cortex; this is the basis of house-training. The detrusor reflex can also be voluntarily initiated (e.g., territorial marking behavior). Patients with cerebral cortical dysfunction typically urinate normally, but will do so in inappropriate locations (loss of learned urination habits). The basal nuclei and preoptic area of the hypothalamus may play a role in the initiation of bladder evacuation. The ventromedial region of the hypothalamus has an inhibitory influence on urination.

B. Cerebellar influence

The influence of the cerebellum on urination appears to be minor. The cerebellum normally exerts an inhibitory influence over the detrusor reflex. Cerebellar lesions may result in increased frequency of urination.

VI. Normal Bladder Filling and Evacuation^{1,2,4-15}

A. Bladder filling (primarily controlled by L region of the pons)

1. As the bladder gradually fills with urine, afferent information is conveyed to neurons in the brain-stem micturition center. As the bladder is not stretched appreciably during this phase, the signal to brain-stem neurons involved in the micturition reflex promotes further bladder filling. Brain-stem neurons involved in facilitating urine storage have the following efferent influences on spinal cord neuronal pools:
 - a. Facilitation of the somatic efferent neuronal cell bodies comprising the pudendal nerve.
 - b. Facilitation of the adrenergic efferent neuronal cell bodies comprising the hypogastric nerve.

- c. Inhibition of the cholinergic efferent neuronal cell bodies comprising the pelvic nerve.
 - 2. The brain-stem micturition center neurons involved in urine storage will remain active until bladder capacity is reached. Until then, the net effects of the above influences are bladder relaxation and urethral constriction.
- B. Bladder evacuation (primarily controlled by M region of the pons)
- 1. When bladder capacity is reached, the resultant stretching of the detrusor muscle produces an afferent "threshold" stimulus. The threshold phenomenon can be compared to an "on/off" switch; once a critical level of stretch or distention is produced in the detrusor muscle, the signal to the micturition center changes to promote bladder emptying. Neurons involved in urinary bladder evacuation have the following efferent influences on the spinal cord neuronal pools involved in urination:
 - a. Inhibition of the somatic efferent neuronal cell bodies comprising the pudendal nerve.
 - b. Inhibition of the adrenergic efferent neuronal cell bodies comprising the hypogastric nerve.
 - c. Facilitation of the cholinergic efferent neuronal cell bodies comprising the pelvic nerve.
 - 2. The net effects of the above influences are bladder contraction and urethral relaxation, resulting in coordinated evacuation of the bladder.

VII. Upper Motor Neuron (UMN) and Lower Motor Neuron (LMN) Bladder Dysfunction^{1,2,6-8,16,19}

A. Upper motor neuron (UMN) bladder dysfunction

- 1. This type of bladder dysfunction is encountered with lesions between the pons and the L7 segment of the spinal cord. Such lesions interfere with or abolish the detrusor reflex. Patients are either completely unable to urinate or cannot effectively accomplish bladder emptying. This is encountered most commonly in patients with severe T3–L3 myelopathies.
- 2. The hallmark of UMN bladder dysfunction is increased tone. This phenomenon may be thought of as a disinhibition of the spinal cord neuronal pools involved in urination. The urethral musculature typically becomes hyperactive and the bladder fills with urine. Upon palpation, the bladder often feels turgid (especially when enlarged) and is difficult or impossible to express manually.

B. Lower motor neuron (LMN) bladder dysfunction

- 1. This type of bladder dysfunction occurs with lesions of the sacral spinal cord or sacral nerves within the vertebral canal (cauda equina area), or with lesions of the pelvic/lumbosacral plexus area within the pelvic canal. These lesions

also attenuate or abolish the detrusor reflex. This type of bladder dysfunction is seen most commonly with traumatic injuries to the caudal lumbar and sacral spine.

2. The hallmark of LMN bladder dysfunction is decreased tone. Both the detrusor and urethral musculature typically become flaccid, and the patient constantly dribbles urine. The bladder is often difficult to discern as an isolated structure (due to the flaccidity), in contrast with the UMN bladder. Slight abdominal pressure usually causes urine to be easily expressed. It is very difficult to tell by palpation, however, if the bladder has been adequately emptied. In some patients, the unattenuated efferent hypogastric nerve activity provides enough internal urethral sphincter tone to make bladder expression difficult.
3. Patients with lesions causing LMN bladder dysfunction often exhibit decreased or absent perineal reflexes and sensation.

VIII. Pharmacologic Manipulation of Bladder Function^{1,2,6-8,16,19,20}

A. Although there exists a multitude of pharmacologic agents that can be employed to manipulate bladder and urethral function, only a few of these drugs are commonly used. The following discussion will focus on those drugs most frequently used in clinical practice.

1. Bethanecol chloride
 - a. This is a parasympathomimetic (cholinergic drug) used to facilitate detrusor muscle contraction in both UMN and LMN bladder dysfunction. Bethanecol directly stimulates cholinergic receptors.
 - b. The dosage is empiric. The oral dose for dogs is 2.5–25 mg (depending on the size of the dog) per dos, every 8 hr. For cats, the dosage is 1.5–5 mg per dos, every 8 hr.
 - c. The half-life of elimination is unknown for dogs and cats. However, most patients seem to have some benefit from the drug within 24 hr, suggesting a relatively short half-life.
 - d. Side effects may occur with this drug and reflect cholinergic overstimulation. Most commonly, gastrointestinal side effects are exhibited. These include anorexia, salivation, vomiting, diarrhea, and abdominal pain. Excessive lacrimation is also a possibility. A cholinergic crisis (e.g., increased bronchial secretions, hypotension) can occur, but is very unlikely with standard doses of this drug.
 - e. Because bethanecol does not cause urethral relaxation, and may even enhance urethral sphincter tone, it is recommended that it not be administered as a sole urinary drug to a patient with the typical UMN bladder (i.e., increased urethral sphincter tone). Bethanecol is contraindicated in patients with suspected or confirmed gastrointestinal or urinary tract obstruction.
2. Diazepam

5. Miscellaneous drugs

Drugs that may be helpful in improving bladder contractility include metoclopramide, cisapride, and propranolol. These drugs should be considered when bethanecol is ineffective. Metoclopramide and cisapride are gastrointestinal prokinetic agents with cholinergic activity. Propranolol is a beta-adrenergic antagonist. The oral dose of metoclopramide for dogs and cats is 0.2–0.5 mg/kg body weight, every 8 hr. Possible side effects of metoclopramide include behavioral abnormalities and constipation. Oral cisapride is administered at a dosage of 0.5 mg/kg body weight, every 8 hr in dogs. The recommended oral dose of cisapride in cats is 1.25–5.0 mg *per cat*, every 8–12 hr. Adverse side effects that may occur with cisapride administration include diarrhea and abdominal pain. Propranolol is dosed orally at 0.2–1.0 mg/kg body weight, every 8 hr in dogs; the oral dose for cats is 2.5–5.0 mg *per cat*, every 8–12 hr. Hypotension, syncope, bronchoconstriction, bradycardia, hypoglycemia, and diarrhea are all potential side effects of propranolol administration.

Several drugs may be helpful in effecting urethral relaxation, in addition to phenoxybenzamine and diazepam. Prazosin, an alpha-adrenergic antagonist, was mentioned earlier. The oral dose of prazosin for dogs is 0.067 mg/kg body weight, every 8–12 hr. The oral dose for cats is 0.25 mg *per cat*, every 12–24 hr. Prazosin can produce marked hypotension. It is recommended that one-half the calculated dose be administered for the first several days of treatment, and the patient observed for clinical signs of hypotension. Baclofen is a spinal-reflex-inhibiting drug that acts by decreasing activity of spinal cord motor neurons and interneurons. The drug has been used in people to cause relaxation of the external urethral sphincter. There is little clinical information concerning the use of baclofen in dogs, and none in cats. The recommended dose for baclofen in dogs is 5–10 mg/kg body weight, every 8 hr. Potential side effects of baclofen include weakness, dizziness, and ptialism. Baclofen use is not recommended in cats. Dantrolene is a muscle relaxant that antagonizes calcium release from skeletal muscle sarcoplasmic reticulum; it has been used to produce relaxation of the external urethral sphincter musculature. The oral dose of dantrolene in dogs is 1–5 mg/kg body weight, every 8 hr. The oral dose in cats is 0.5–2.0 mg/kg body weight, every 8 hr. Potential side effects of dantrolene administration include sedation, gastrointestinal upset, dizziness, generalized muscle weakness, hypotension, and hepatotoxicity. Long-term dantrolene administration is not recommended, due primarily to the chance of severe hepatotoxicity.

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Chapter 12

DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM: MONONEUROPATHIES AND POLYNEUROPATHIES

Curtis W. Dewey

I. Introduction

The peripheral nerves are made up of myelinated and unmyelinated motor and sensory axons, and are essential for normal functioning of both the voluntary and autonomic nervous systems. Some neuropathies are characterized by exclusively or primarily motor dysfunction, others by sensory dysfunction, and some by a combination of motor and sensory dysfunction. Some of the salient features of autonomic neuropathies in dogs and cats have only recently been described. Technically speaking, a mononeuropathy refers to dysfunction of one cranial nerve (e.g., facial nerve) or one named peripheral nerve (e.g., radial nerve). A polyneuropathy refers to multiple (i.e., more than one) nerve dysfunction. In this text, multiple cranial nerve dysfunction (without dysfunction of peripheral nerves to the limbs) and multiple peripheral nerve dysfunction in the same limb (e.g., brachial plexus neuropathy/neuritis) will be referred to as multiple mononeuropathies. This distinguishes these relatively focal disorders from more generalized polyneuropathies (e.g., idiopathic polyradiculoneuritis).

In general, neuropathies reflect a failure of the lower motor neuron (LMN). Although some of the diseases discussed in this chapter have abnormal axons and/or myelin in both the central (CNS) and peripheral (PNS) nervous systems, clinical signs of peripheral disease usually predominate. In those neuropathies in which motor nerves are affected, typical clinical signs include decreased to absent reflex activity, poor muscle tone, and neurogenic muscle atrophy. A recurring theme with canine and feline neuropathies is that tentative diagnoses are often based upon a combination of clinical features that are characteristic for specific diseases. Electrodiagnostic and nerve/muscle biopsy evidence may confirm the presence of a neuropathy, but rarely provides a specific diagnosis by itself. Even when a specific disease entity is confirmed histopathologically (e.g., dysautonomia), the underlying etiology often remains undetermined. Indeed, the underlying cause(s) of the majority of canine and feline neuropathies is (are) unknown. For many of these disorders, therefore, there are no effective treatments. However, some of these disorders resolve spontaneously, and others may not necessarily adversely affect the quality of the patient's life.

It is important that the clinician be able to localize disorders to the peripheral nervous system. The multitude of reported neuropathies may seem intimidating, but a working knowledge of all these disorders is unnecessary. Once the neuroanatomic diagnosis is made (peripheral nervous system), appropriate reference sources should be consulted in an attempt to arrive at a specific diagnosis. Knowing that there is a wide spectrum of neuropathies, with different causes, severities, and prognoses, is

important both to patient management and client communication. Disorders of cranial nerve VIII (hearing and balance) are discussed in Chapter 7 and will not be discussed in this chapter.

II. Disorders of Peripheral Nerves in Dogs and Cats (see Table 12.1)

A. Degenerative¹⁻³

1. Hereditary polyneuropathy of Alaskan malamutes (HPAM)/Idiopathic polyneuropathy of Alaskan malamutes (IPAM).
 - a. HPAM refers to dogs from Norway, while IPAM refers to dogs recently described from the United States. Although there are some differences between the two groups of dogs, they are considered together in this text because of their many clinical similarities. Believed to be an autosomal recessively inherited trait, this disease is characterized by widespread degeneration of axons and myelin. The pathogenesis is unknown.
 - b. Clinical signs typically begin at 12–18 mo of age, and consist initially of pelvic limb paresis and ataxia and reduced exercise tolerance. Progression of the disease is variable, but worsening paraparesis or tetraparesis, as well as regurgitating and coughing (due to megaesophagus, laryngeal paresis/paralysis, and aspiration pneumonia) may develop. Spinal reflexes are usually depressed or absent, and moderate to severe muscle atrophy may be appreciated, especially in the shoulder and thigh areas.
 - c. Diagnosis is based upon history, signalment, and typical clinical features, as well as abnormal results of electrodiagnostic tests, nerve/muscle biopsies, and/or upon histopathologic findings postmortem.
 - d. The disease is typically progressive and there is no known treatment. The prognosis for short-term survival varies from favorable to poor, as some dogs will improve, whereas others will progressively worsen. In general, the dogs that improve tend to do so transiently, and often die or are euthanized due to recurrence of clinical signs (e.g., paresis, respiratory problems, regurgitation).
2. Boxer dog progressive axonopathy^{1,4-9}
 - a. This is an autosomal recessively inherited trait characterized by widespread degeneration of myelin and multiple axonal swellings (spheroids) in both motor and sensory axons of the central and peripheral nervous systems. The pathogenesis is unknown, but is suspected to involve faulty axonal transport mechanisms, with resultant accumulations of neurofilaments and membranous organelles (constituents of the spheroids) along the axon. It is thought that this disease is primarily an axonopathy, with secondary demyelination.
 - b. Age of onset of clinical signs is typically 2–6 mo of age (usually 2–3 mo). Pelvic limb ataxia and hypermetria are initially exhibited and this abnormal gait remains the salient clinical feature throughout the course of disease progression. Spinal reflexes other than withdrawal reflexes are

Table 12.1: Neuropathies of Dogs and Cats

Degenerative	Anomalous/ Developmental	Metabolic	Neoplastic	Inflammatory/ Infectious, Autoimmune	Traumatic	Toxic
Alaskan Malamute polyneuropathy	Optic nerve hypoplasia	Diabetic neuropathy	Paraneoplastic neuropathies	Brachial plexus neuritis/ neuropathy	Isolated nerve injury	Thallium poisoning
Boxer dog axonopathy		Hyperadreno- corticoid neuropathy	Malignant nerve sheath tumors	Optic neuritis	Compartment syndrome	Pyridoxine poisoning
Birman cat polyneuropathy		Hyperchylo- micronemia (cats)	Mononuclear cell neoplasia (myelomonocytic neoplasia, lymphosarcoma)	Polyradiculo- neuritis	Brachial plexus injury	Vincristine neuropathy
Laryngeal paralysis/ polyneuropathy complex		Hyperoxaluria (cats)		Chronic inflammatory demyelinating polyneuropathy/ chronic relapsing polyneuropathy		Delayed organophosphate toxicity (cats)
Dancing Doberman disease		Hypothyroid neuropathy				Walker hound mononeuropathy
Idiopathic facial paralysis						Salinomycin toxicity (cats)
Giant axonal neuropathy						
Golden retriever hypomyelinating polyneuropathy				Protozoal polyradiculo- neuritis		
Hypertrophic neuropathy				Sensory ganglio- radiculoneuritis		
Laryngeal paralysis				Trigeminal neuritis		
Megaesophagus				Hemifacial spasm		
Distal sensorimotor neuropathy				Ischemic neuromyopathy		
Sensory neuropathy						
Idiopathic self-mutilation						
Spinal muscular atrophy						
Dysautonomia						
Distal denervating disease						
Lysosomal storage disease						

decreased or absent and decreased muscle tone is apparent. Ataxia and paresis slowly progress and may also involve the thoracic limbs. Conscious proprioception (e.g., proprioceptive positioning/placing) is often normal initially, but deteriorates over time. Pain sensation (nociception) remains intact. Mild signs of cerebellar dysfunction (ocular tremors, head-bobbing) have been described in a few dogs, late in the course of the disease. Muscle atrophy is typically minimal to nonexistent with this disease.

- c. A tentative diagnosis can be made based upon signalment, historical and clinical findings, as well as abnormal results of electrodiagnostic testing and nerve/muscle biopsies. Definitive diagnosis requires demonstration of characteristic histopathologic abnormalities (e.g., spheroids) in both the peripheral and central nervous systems.
 - d. The prognosis is variable. There is no treatment for this disorder, but some dogs will stabilize by 12–18 mo of age and the clinical signs will remain relatively static for months or even years. Most of these dogs are eventually euthanized due to inability to ambulate.
3. Birman cat distal polyneuropathy^{1,4,5,10,11}
- a. This is a disease of Birman kittens of suspected autosomal recessive inheritance. Loss of myelin and axons of the PNS and CNS results in clinical signs of disease. The lesions are most severe in the distal portions of axons, suggesting a dying-back process. Axonal integrity depends upon anterograde transport of substances (e.g., proteins) from the neuronal cell body throughout the length of the axon, and retrograde conveyance of cellular waste products from the axon back to the cell body to be degraded. Disease processes that adversely affect either the neuronal cell body or axonal transport mechanisms will likely have most serious consequences on the distal-most aspect of the axon. As the disease process continues, axonal degeneration will proceed proximally, “dying back” toward the neuronal cell body. The pathogenesis of Birman cat distal polyneuropathy is unknown.
 - b. Affected kittens exhibit clinical signs of neurologic dysfunction at approximately 8–10 wk of age. Pelvic limb ataxia and paresis (with frequent falling episodes), subtle hypermetria of all four limbs, and plantigrade stance in the pelvic limbs are characteristic clinical features of the disorder. Kittens with this disorder also tend to adduct the pelvic limbs.
 - c. Tentative diagnosis is based upon signalment, historical and clinical findings, and results of diagnostic tests (e.g., electromyography, nerve/muscle biopsy). Definitive diagnosis is based upon histopathology of the CNS and PNS lesions.
 - d. There is no known treatment for this progressive disease and the prognosis is poor.
4. Laryngeal paralysis-polyneuropathy complex^{1,4,5,12–16}
- a. This disorder is characterized by widespread loss of peripheral axons (axonal necrosis), especially in distal segments, in young (usually 2–6-mo-

old) Dalmatian and Rottweiler dogs. The pathogenesis is unknown, and an autosomal recessive mode of inheritance is suspected. This disease is thought to involve a dying-back process of axons, affecting distal segments of axons most severely. Sixteen Dalmatians and five Rottweilers have been reported with this disorder. A similar disorder was recently described in nine young, male Leonberger dogs in the United States (six dogs) and Belgium (three dogs). An X-linked mode of inheritance is suspected in this breed.

- b. Onset of clinical signs is typically from 2–6 mo of age in Dalmatians and Rottweilers; clinical signs of dysfunction became apparent between 1 and 3 yr in the Leonberger dogs. Common to all three reported breeds are clinical signs relating to laryngeal paralysis, including respiratory distress (e.g., inspiratory stridor, coughing, cyanosis, dyspnea) with associated exercise intolerance, and voice change (dysphonia). Limb paresis (worse in the pelvic limbs in Rottweilers) with hyporeflexia is also a consistent clinical feature. Gagging, regurgitation (megaesophagus was identified in 9 of 16 Dalmatians), facial paralysis, lingual paralysis, hypermetric gait, and muscle atrophy are additional clinical signs associated with the Dalmatian disease. Hip and stifle hyperflexion while ambulating was a characteristic gait abnormality in the Leonberger dogs. These dogs also tended to “throw” the foot forward during the pelvic limb swing phase. One of five Rottweiler puppies displayed regurgitation associated with megaesophagus. A peculiar finding in the Rottweilers was bilateral cataracts in four of the five dogs; the cause of these cataracts was undetermined.
 - c. A tentative diagnosis of this disorder is based upon signalment, history, characteristic clinical findings, and abnormal results of diagnostic tests (e.g., electrodiagnostics, nerve/muscle biopsies). Definitive diagnosis of this disorder is based upon the character and distribution of axonal lesions identified postmortem.
 - d. There is no treatment for this disorder. The prognosis is poor, as most dogs die or are euthanized shortly after presentation due to respiratory dysfunction, often involving severe aspiration pneumonia.
5. Dancing Doberman disease^{1,14,17}
- a. This is a recently described enigmatic peripheral nervous system disorder, principally affecting the gastrocnemius muscles, which occurs in Doberman Pinschers. Clinical and pathological features suggestive of both a neuropathy and a myopathy have been described. To date, it is unclear whether this syndrome is primarily a myopathy, a neuropathy, or some combination of the two.
 - b. Age at onset of clinical signs of dysfunction has ranged from 6 mo to 7 yr. The first observable abnormality is flexing of one pelvic limb while standing (Fig. 12.1). Within several months, these dogs typically will begin alternately flexing and extending both pelvic limbs when standing, giving the appearance of dancing. Affected dogs often prefer to sit, rather than

affected. Cats with hypertrophic neuropathy display generalized tremors that worsen with activity, hypermetric gait, plantigrade stance, depressed spinal reflexes, and decreased sensation in the facial region and extremities. Mild limb paresis and muscle atrophy may also be appreciated.

- c. Diagnosis of this condition is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic tests and nerve/muscle biopsies.
 - d. There is no treatment for this progressive disease and the prognosis is poor.
10. Laryngeal paralysis^{1,4,5,18,36–48}

- a. This refers to a motor neuropathy of the recurrent laryngeal nerve that appears to occur in two major forms. The first form is a hereditary disease of immature animals (less than 12 mo of age) and the second form is an acquired (also referred to as idiopathic laryngeal paralysis) disorder of middle-aged to older dogs and cats. Both forms appear to be much more common in dogs than cats. In both disorders, denervation atrophy of the cricoarytenoideus dorsalis muscle and axonal and myelin loss in the recurrent laryngeal nerve(s) are characteristic features. The pathogenesis is unknown for both forms of laryngeal paralysis. Specific information pertaining to the two forms of this neuropathy is as follows:

- (1) Hereditary laryngeal paralysis—this is best described for the Bouvier des Flandres breed, in which the disease is inherited as an autosomal dominant trait. Recurrent laryngeal nerve degeneration is due to neuronal degeneration in the nucleus ambiguus of the brain stem. Onset of clinical signs is typically between 4 and 6 mo of age. However, age of onset of clinical signs has been reported up to 7 yr of age in this breed. A similar disease has been described in young Siberian Husky and Husky-crossbred dogs, Bull terriers, Rottweilers, and white-coated German Shepherd dogs.
 - (2) Acquired (idiopathic) laryngeal paralysis—this is encountered most commonly in older, large- and giant-breed dogs such as Labrador retrievers, Saint Bernards, Irish setters, and Afghan hounds. There appears to be no breed or sex predilection for cats with laryngeal paralysis. The median age of cats with laryngeal paralysis was reported as 11 yr in one study.
- b. Clinical signs reflect dysfunction of the arytenoid cartilages and vocal folds and include dysphonia, inspiratory noise (stridor), and respiratory distress (especially when exercising). Retching, gagging, and coughing associated with eating and drinking may also be appreciated. Concurrent megaesophagus has been reported with laryngeal paralysis in a small percentage of both canine and feline cases. Clinical signs tend to progress in severity over several months.
 - c. Both forms of this neuropathy are diagnosed by historical and clinical features and by ruling out other causes of laryngeal paresis/paralysis (e.g., neuromuscular junction disorders, hypothyroidism). Abnormal EMG

- b. The dogs reported with this disease ranged in age from 1.5 to 4 yr at the time of clinical disease onset. The clinical course consists of paraparesis initially, that slowly progresses to tetraparesis, with hyporeflexia and hypotonia, and atrophy of distal limb muscles. The disease is typically slowly progressive (sometimes over a year) and may even wax and wane. Dogs with distal symmetric polyneuropathy may exhibit decreased nociception and masticatory muscle atrophy.
 - c. Diagnosis is based upon signalment, historical and clinical findings, and abnormalities noted on electrodiagnostic testing (especially EMG of distal limb muscles) and nerve/muscle biopsies.
 - d. Some dogs seem to transiently respond to glucocorticoid therapy, but this is a progressive disease with no known treatment. The long-term prognosis is guarded to poor.
13. Sensory neuropathy of longhaired Dachshunds^{1,4-6,62,63}
- a. Believed to be inherited as an autosomal recessive trait, this disorder is characterized by degeneration of principally distal sensory axons in both the PNS and CNS. The pathogenesis of this disorder is unknown. A similar disorder has been reported in a Jack Russell terrier and a Border collie.
 - b. Clinical signs of dysfunction may be evident by 8–12 wk of age and include mild ataxia, loss of proprioception (especially in the pelvic limbs), and widespread reduction or loss of superficial and deep pain perception. Some patients may exhibit vomiting and/or urinary incontinence, presumably due to degenerative changes in the autonomic nervous system. Self-mutilation may also be exhibited. There is no evidence of muscular atrophy in these dogs, and spinal reflexes may be normal or slightly reduced.
 - c. Diagnosis is made via history, signalment, and clinical findings, along with results of electrodiagnostic testing (decreased to absent sensory nerve potentials) and muscle/nerve biopsy.
 - d. Despite the fact that there is no treatment for this disorder, patients can live relatively normal lives.
14. Sensory neuropathy of Pointer dogs^{1,4-6,62,64-66}
- a. An autosomal recessively inherited sensory polyneuropathy has been reported in English pointer dogs as well as Czechoslovakian shorthaired pointer dogs. The pathogenesis is unknown, but the disease is characterized by loss of sensory neurons (as well as their axonal processes and myelin) and an associated lack of an important nociceptive neurotransmitter called substance P.
 - b. Clinical signs typically become apparent between 2 and 12 mo of age. There is loss of pain perception to the distal aspect of the paws (e.g., the toes) and decreased pain sensation proximal to the carpus and tarsus. There is the possibility that paresthesia/ dysesthesia may contribute to the clinical picture. The dogs begin to lick and then chew their digits, ultimately leading to autoamputations (Fig. 12.4). Apparently painless frac-



Fig. 12.4. Automutilation of the digits in a Pointer dog with sensory neuropathy (Courtesy of Dr. Jacques Penderis).

- tures and osteomyelitis of the paw may occur. There are no other neurologic deficits, other than altered pain perception to the distal limbs.
- c. A tentative diagnosis is usually based upon history, signalment, clinical findings, and, potentially, nerve biopsy results. Results of electrodiagnostic tests are normal in this disease. Definitive diagnosis is based upon histopathologic evaluation of spinal ganglia, axonal processes of the sensory nuclei of those ganglia (both in the PNS and CNS), and a lack of staining for substance P in the spinal cord.
 - d. There is no effective treatment for this disorder and the prognosis is poor.
15. Idiopathic self-mutilation^{4,18,67-69}
- a. Also known as *acral lick dermatitis*, this self-mutilatory behavior of “high-strung” breeds of dogs and cats (e.g., Doberman Pinschers, German Shepherd dogs, Siamese and Abyssinian cats) may be due to a mild sensory polyneuropathy. There is electrophysiologic and histopathologic evidence to support this theory. The pathogenesis of this suspected sensory polyneuropathy is unknown.
 - b. Clinical signs of this disorder are usually limited to licking, biting, or scratching an area of skin around the tarsal or carpal areas.
 - c. Diagnosis of this syndrome is typically based on typical historical and clinical findings in a “nervous” or “high-strung” pet. Other dermatologic conditions should be ruled out. Some patients will respond (decreased self-mutilatory behavior) to the tricyclic antidepressant drug clomipramine, at a dose of 1–3 mg/kg per os, per day. Secondary skin infections should be treated with appropriate antibiotic regimens.
 - d. The prognosis for control of this condition is good.
16. Spinal muscular atrophy (SMA)^{1,4,5,70-89}
- a. Spinal muscular atrophy (SMA) represents a spectrum of uncommon disease syndromes characterized by premature degeneration of motor neurons primarily in the spinal cord and, to a variable degree, the brain stem.

There are multiple forms of SMA, described in a number of dog breeds, with various clinical presentations and levels of severity. In some forms of the disease, there may also be cerebellar neuronal degeneration. It is currently not clear as to whether or not all of these disorders belong in the same category (e.g., SMA) or if some should be classified as multisystem neuronal degeneration.

Most of these disorders appear to be analogous to infantile spinal muscular atrophy of humans, with onsets of dysfunction occurring during the first several weeks to months of life. Adult-onset SMA, similar to amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) of people and equine motor neuron disease, is rarely reported in dogs and cats. Recently, however, adult-onset SMA was reported in three cats. The pathogenesis is unknown, but SMA is believed to represent an abiotrophy, or premature cell death. These disorders are suspected or proven, depending upon the specific disorder, to be autosomally-inherited traits. In the most completely studied form of this disease syndrome, hereditary SMA of Brittany spaniels (autosomal dominant inheritance), there is evidence that both abnormal cytoskeletal neuronal protein production (e.g., neurofilaments) and imbalances of excitatory CNS neurotransmitters (e.g., aspartate, glutamate) are linked to premature neuronal cell death.

- b. Spinal muscular atrophy has been reported in numerous breeds, including Brittany spaniels, English pointer dogs, German Shepherd dogs, Rottweilers, Swedish Lapland dogs, Great Dane crossbred dogs (Stockard's paralysis), Cairn terriers, Griffon Briquet Vendé' en dogs, a Saluki, and several cats. The typical clinical picture is that of a rapidly progressing polyneuropathy (LMN paresis) in the first 1–6 mo of life, mainly or exclusively affecting the limbs. Paresis with decreased to absent spinal reflexes and neurogenic muscle atrophy usually progresses to paralysis within weeks. Pelvic limb paresis typically occurs prior to thoracic limb paresis. Limb joints may become malpositioned and immovable, subsequent to pronounced muscle atrophy. Some dogs have a more protracted disease course, with less severe signs. For example, the German Shepherd dog disease appears to be an asymmetric, focal loss of motor neurons in the cervical intumescence, with relatively static unilateral or bilateral thoracic limb dysfunction. The accelerated (homozygous) form of the Brittany Spaniel SMA follows the typical pattern of early onset and rapid disease progression. However, the intermediate form has an onset at 6–12 mo of age and progresses slowly to tetraparesis by 2–3 yr of age, and the chronic form has the same age at onset as the intermediate form, but is nearly subclinical.

Some breeds will exhibit signs of brain-stem (e.g., dysphonia, megaeosophagus, tongue fasciculations) or cerebellar (e.g., head tremor) dysfunction, in addition to the lower motor neuron signs to the limbs. Apparent cataplectic episodes have been observed in the Cairn terrier disease. This disorder may belong in the category of multisystem neuronal degeneration (see Chapter 4), rather than SMA.

drops of dilute (0.05%–0.1%) pilocarpine. These patients also tend to exhibit improved ability to urinate after subcutaneous administration of a low dose (0.04 mg/kg) of bethanecol. Definitive diagnosis requires demonstrating neuronal cell loss in the parasympathetic nervous system postmortem.

- d. There is no specific treatment for this disease, and spontaneous clinical recoveries are uncommon. Recovery has been reported in cats. However, this recovery may not begin to be apparent for several months and may take a prolonged period of time. During this convalescent time, intensive nursing care, including tube-feeding, bladder expression, enemas, correction/prevention of electrolyte abnormalities and dehydration, and anti-emetic administration (e.g., metoclopramide) may be required of the owner. Survival of severely affected cats has been estimated to be between 25% and 50% with such supportive treatment. Most patients with dysautonomia either die or are euthanized due to complications of the disease.

18. Distal denervating disease^{1,4,6,18,106}

- a. A motor polyneuropathy of unknown pathogenesis has been reported in dogs in the United Kingdom. Lesions are restricted to degeneration of distal axons and myelin of motor nerves.
- b. There is no age, sex, or breed predisposition. Clinical signs of a LMN tetraparesis (hypotonia, decreased to absent spinal reflexes) develop over a period of 1 wk to 1 mo. Signs of cranial nerve dysfunction may also occur, including dysphonia, facial weakness, and atrophy of masticatory muscles. There is no evidence of sensory dysfunction. Atrophy of proximal limb muscles is characteristic. Respiration, swallowing, and bladder control remain unaffected. Most dogs recover fully with supportive care within 4–6 wk.
- c. Diagnosis is based upon clinical findings, and abnormal results of electrodiagnostic tests and nerve/muscle biopsies. Treatment is supportive.
- d. The prognosis is favorable, as most dogs recover fully within 4–6 wk.

19. Lysosomal storage diseases^{1,4–6,11,107}

- a. Some of the lysosomal storage diseases discussed in Chapter 4 can have peripheral polyneuropathy as part of the clinical syndrome. In some cases, a peripheral polyneuropathy can be the only clinical abnormality (e.g., Niemann-Pick disease in Siamese cats). The lysosomal storage diseases that may include signs of polyneuropathy as part of the clinical picture include the following:
 - (1) Fucosidosis—a glycoproteinosis of English Springer Spaniels.
 - (2) Globoid cell leukodystrophy (Krabbe's disease)—a sphingolipidosis most common in West Highland White and Cairn terriers.
 - (3) Glycogen storage disease type IV—a glycogenosis reported in Norwegian Forest cats.
 - (4) Niemann-Pick disease—a sphingolipidosis reported in Siamese cats.
- b. Clinical signs for most of these disorders reflect multifocal disease of the nervous system. Tentative diagnosis is based upon historical and clinical

findings, abnormal electrodiagnostic test results, and lesions supportive of the suspected disorder in muscle/nerve biopsies. Diminished enzyme activity (of the suspected enzyme of interest) in leukocytes, skin biopsies, or cultured cells (e.g., skin fibroblasts, hepatocytes) may be used as a confirmatory diagnostic test in some of these disorders.

- c. There is no treatment for these progressive diseases, and the prognosis is poor.

B. Anomalous/developmental: Optic nerve hypoplasia^{4,108–112}

1. This idiopathic congenital condition is uncommonly reported in dogs and rare in cats. There is a lack of neurons in the ganglion layer of the retina and atrophy of the optic nerve. Other concurrent ocular abnormalities (retinal dysplasia, retinal detachment) have been reported. Optic nerve hypoplasia can occur either unilaterally or bilaterally.
2. This condition is believed to be a heritable trait in miniature Poodles. It has been reported in a number of different breeds, however. Diagnosis is based upon a history of visual problems since opening of the eyelids in infancy, clinical signs of blindness, mydriasis, and absent direct pupillary light reflex on the affected side(s), and ophthalmoscopic findings of a small optic disk on the affected side(s).
3. The visual deficits are permanent and there is no treatment for this congenital condition. These patients will, however, make acceptable pets.

C. Metabolic

1. Diabetic neuropathy^{1,4,11,108,113–122}

- a. A polyneuropathy associated with diabetes mellitus has been described in both dogs and cats. The prevailing thought has historically been that this neuropathy primarily reflects a distal (dying back) axonopathy with secondary demyelination/remyelination. However, more recent evidence suggests that abnormal Schwann cell/myelin function may play a pivotal role in the development of diabetic neuropathy, with axonal damage being comparatively less important. The pathogenesis of axonal and Schwann cell/myelin dysfunction is unknown, but several hypotheses exist. It is likely that certain aspects of all these hypotheses act in concert to effect peripheral nerve dysfunction. The three hypotheses include the following:
(1) Vascular hypothesis—microvascular disease is known to occur with diabetes mellitus. The mechanisms responsible for microvascular compromise are not clearly defined, but may include: decreased vasodilatory molecules (e.g., prostacyclin, prostaglandin E₁) and increased vasoconstrictive molecules (e.g., thromboxane A₂, endothelin) in vascular endothelium, due to altered lipid metabolism; abnormally functioning hemoglobin and 2,3-diphosphoglycerate, due to protein glycosylation; and thrombosis subsequent to altered vessel compliance (accumulation of glycosylated molecules in and around endothelial cells) and increased red blood cell and platelet aggregation (altered



Fig. 12.5. Characteristic pelvic limb posture of a cat with diabetic neuropathy (Courtesy of Dr. Gregg Kortz).

- c. Diagnosis depends upon confirming the presence of a polyneuropathy in a patient with diabetes mellitus, and ruling out other likely causes of polyneuropathy. Abnormalities are typically found with electrodiagnostic test results and muscle/nerve biopsies, supporting the diagnosis.
- d. Currently, there is no specific therapy proven effective for improving the polyneuropathy, but spontaneous resolution may occur after control of the diabetic condition is achieved. The prognosis remains guarded, however, since patients may not recover function, even with adequate diabetic control.
2. Hyperadrenocorticoid (Cushing's) neuropathy^{4,108}
 - a. There is recent evidence of an association between hyperadrenocorticism and polyneuropathy in dogs. Some, not all, of these dogs, had concurrent hyperadrenocorticoid myopathy (see Chapter 13). The pathogenesis is unknown.
 - b. There is currently little knowledge available concerning the typical clinical features and prognosis for recovery for this suspected endocrine neuropathy.
3. Hyperchylomicronemia in cats^{1,4,6,11,108,123-125}
 - a. This is a deficiency of the hormone *lipoprotein lipase*, that is believed to be inherited as an autosomal recessive trait. Accumulations of granulomatous masses of lipid and coagulated blood (xanthomas) accumulate in various tissues. The xanthomas in the nerve roots and peripheral nerves cause a compressive neuropathy, with loss of axons and myelin.
 - b. Affected cats may have fasting hyperlipemia, giving their blood a "cream of tomato soup" coloration. Lipemia retinalis, a pallid appearance to the retinal vasculature apparent on fundoscopic examination, is a consistent clinical feature of this disease. Signs of polyneuropathy do not typically occur until about 8 mo of age. A wide variety of neurologic abnormalities may be identified, including Horner's syndrome, paresis/paralysis of the

ropathy are diverse and include paresis or paralysis of cranial nerves (CN) V, VII, and VIII (alone or in combination), laryngeal paresis/paralysis, megaesophagus, and LMN paresis/paralysis of the limbs. An association between hypothyroidism and acquired myasthenia gravis (Chapter 14) may exist in dogs. Since many of the clinical signs for these two disorders are similar, both disorders should be ruled out in suspect cases.

- c. Diagnosis is based upon confirming the existence of hypothyroidism in a dog with a neuropathy. The presence of a neuropathy can be confirmed in many cases, based upon abnormal results of electrodiagnostic tests and muscle/nerve biopsies. Proving a dog to be truly hypothyroid may be more problematic. The standard method is demonstrating a subnormal response to exogenously administered thyroid stimulating hormone (TSH response test). TSH is expensive and often difficult to obtain. Also, some test results fall into a "grey zone" that may or may not be supportive of hypothyroidism. Measuring free thyroxine (free T_4) levels by equilibrium dialysis is believed to be a relatively accurate assessment of thyroid functional status. Concurrently measuring serum TSH levels has been suggested, with elevated TSH levels expected in cases of primary hypothyroidism. A clinically acceptable method of tentatively diagnosing hypothyroid neuropathy is response to thyroid supplementation therapy in a suspect patient (neuropathy with a low resting T_4 level).
- d. Treatment of hypothyroid neuropathy involves supplementation with oral thyroxine (20 $\mu\text{g}/\text{kg}$, q 12 hr) and supportive care specific to the neuropathy exhibited by the patient (e.g., gastrostomy tube feeding in the megaesophagus patient). Prognosis is generally guarded to good for clinical recovery.

D. Neoplastic

1. Paraneoplastic neuropathies^{1,4,6,108,133-137}

- a. Both subclinical and clinical mononeuropathies and polyneuropathies have been associated with various neoplasms. These neuropathies are believed to develop as an indirect rather than a primary effect of the underlying neoplasia. The pathogenesis of this phenomenon is unknown, but several hypotheses exist. Potential explanations include elaboration of some neurotoxic factor by the tumor, disruption of axonal and/or Schwann cell metabolism by the tumor, and an immunologic reaction to antigens shared by the neoplasm and peripheral nerve elements (i.e., innocent bystander reaction). A paraneoplastic polyneuropathy has been reported occasionally with pancreatic insulinomas, and the potential exists for the associated hypoglycemia to be responsible for the neuropathy. However, peripheral nerves are particularly resistant to the effects of hypoglycemia and peripheral neuropathy has not been associated with any other disease that results in hypoglycemia. The hypoglycemia may not be a major contributing factor to the neuropathy, or some other effect of the

- syndrome. If the intracranial portion of CN V is involved, other signs of brain-stem dysfunction may develop over time (due to compression).
- c. A tentative diagnosis is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic testing, imaging, and possible CSF analysis (usually if imaging is performed). MNSTs of the brachial plexus can sometimes be difficult or impossible to diagnose with these various tests. If results of extensive diagnostics are unrewarding in a patient that is exhibiting signs consistent with a brachial plexus MNST, the next diagnostic step is surgical exploration of the brachial plexus. The typical appearance of an MNST that involves the spinal cord is that of an intradural/extramedullary mass. CT and MRI offer the potential of imaging both the axillary portion and the spinal portion of a brachial plexus MNST, as compared with myelography (Fig. 12.6). CT/myelography combination may also be a valuable imaging option for this disease. CT or (preferably) MRI are the imaging modalities of choice for evaluating MNSTs of cranial nerves (e.g., CN V).
 - d. Definitive treatment for MNST, regardless of location, involves surgical removal of the neoplasm. The responsiveness of these sarcomatous tumors to radiation therapy is unknown. Although there are sporadic reports of long-term survival following surgical removal of these tumors, the overall prognosis is poor. MNSTs tend to recur after surgical removal. Surgical removal of brachial plexus MNSTs usually involves amputation of the affected limb with or without a laminectomy procedure (depending upon whether or not there is tumor invasion into the vertebral canal). However, the median disease-free interval after surgery for these dogs is extremely short, especially when there is spinal cord involvement (approximately 1 mo).



Fig. 12.6. Transaxial MR image (T2-weighted) of a large mass invading the cervical spinal cord. The mass was suspected to be a malignant nerve sheath tumor.

immunogens as dietary horse meat and modified-live rabies vaccines have been made in the few reported veterinary cases. Axonal and myelin loss are thought to be mainly confined to ventral branches of the spinal nerves comprising the brachial plexus.

- b. The typical clinical scenario is a patient with acute onset of bilateral LMN paresis or plegia involving the thoracic limbs. Neurogenic atrophy of thoracic limb muscle is also characteristic. One reported dog also had evidence of unilateral facial paresis.
 - c. A tentative diagnosis is based upon historical (e.g., history of exposure to a possible immunogen) and clinical findings. Electrodiagnostic testing and muscle/nerve biopsies should also support the diagnosis.
 - d. Due to its rarity, little is known about the prognosis of this disorder. In the few cases reported, recovery appears to be prolonged. A prolonged recovery time is typical in the human form of this disease, probably due to the proximal nature of the axonal injury. There is no known specific treatment for this disorder, but glucocorticoid therapy and diets devoid of beef and horse meat (e.g., poultry based) have been suggested.
2. Optic neuritis^{4,18,151,152}
- a. Optic neuritis refers to inflammation of the optic nerves, optic chiasm, and /or optic tracts and exists either alone as an idiopathic (presumably immune-mediated) form or as one manifestation of a more widespread inflammatory/infectious (e.g., GME, canine distemper, fungal disease, protozoal disease, FIP) or neoplastic (e.g., lymphosarcoma) disorder. The pathogenesis of idiopathic optic neuritis is unknown.
 - b. Optic neuritis can occur in both dogs and cats (less common) of both sexes at any age (usually adults). The characteristic clinical findings are acute blindness (usually bilateral) with dilated pupils that are unresponsive to light. Ophthalmoscopic abnormalities (e.g., swollen optic disk) may or may not be evident, depending upon the location of the lesion with respect to the fundus. A normal electroretinogram (ERG) is supportive of optic neuritis, rather than retinal disease. The presence of neurologic deficits other than optic nerve dysfunction suggests that the optic neuritis is not a primary idiopathic condition.
 - c. Diagnosis is based upon historical and clinical findings, ERG results, and tests for possible underlying disorders (e.g., CSF analysis, fungal titers).
 - d. Treatment depends upon the underlying disorder. If infectious and neoplastic processes are ruled out, treatment usually consists of immunosuppressive prednisone therapy (1 mg/kg per os, q 12 hr) for 2 wk (longer if GME is suspected), with subsequent gradual tapering of the dose. Early institution of immunosuppressive therapy is important for a favorable prognosis in idiopathic optic neuritis. Prognosis for return of vision is guarded.
3. Acute idiopathic polyradiculoneuritis (coonhound paralysis, idiopathic polyradiculoneuritis)^{1,4,6,11,108,153-164}

5. Chronic inflammatory demyelinating polyneuropathy (CIDP)/chronic relapsing polyneuropathy^{4,108,167-170}
 - a. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a suspected autoimmune polyneuropathy of mature dogs and cats (mean age of 6–7 yr) that has recently been described. An analogous neuropathy occurs in people. This disorder is believed to be one of the more common neuropathies in dogs and cats. A polyneuropathy very similar to CIDP, referred to as chronic relapsing polyneuropathy, has been described in cats.
 - b. Clinical signs of insidiously progressive LMN paresis, with abnormal proprioception and normal sensation have been described in CIDP and chronic relapsing polyneuropathy. The course of the disease is typically chronic, and patients tend to spontaneously recover and relapse. Clinical signs of dysfunction often occur in the pelvic limbs initially, then progress to involve the thoracic limbs. The spectrum of potential clinical signs of dysfunction is broad and may include depressed spinal reflexes, muscle atrophy, paraparesis, tetraparesis, and tetraplegia.
 - c. Diagnosis is based upon historical and clinical features consistent with the disease, in conjunction with nerve/muscle biopsy results. Response to therapy (see below) also contributes to diagnosis. The predominant pathologic feature seen in nerve biopsies from these patients is evidence of demyelination and remyelination. Inflammatory cells have consistently been identified in ultrastructural studies of nerve biopsies from CIDP patients. Evidence of inflammation was lacking in nerve biopsies from patients with chronic relapsing polyneuropathy. Axonal degeneration is not a feature of CIDP, but was evident on nerve biopsy of one cat with chronic relapsing polyneuropathy.
 - d. The prognosis is guarded to good. Most animals with CIDP and chronic relapsing polyneuropathy tend to be responsive to glucocorticoid therapy. In a recent report, 90% of dogs and 88% of cats with CIDP exhibited an initial positive response to oral prednisone therapy (1–2 mg/kg body weight, every 12 hr). Patients may relapse coincident with reduction of glucocorticoid dosage or discontinuation of glucocorticoid therapy. Some animals that initially respond to glucocorticoid therapy may subsequently become resistant to such treatment. If a positive response to glucocorticoid therapy is demonstrated in a patient with suspected CIDP or chronic relapsing polyneuropathy, dose reduction should proceed slowly once remission of clinical signs is achieved.
6. Protozoal polyradiculoneuritis^{1,4,6,18,171-176}
 - a. Both *Toxoplasma gondii* and *Neospora caninum* produce a severe polyradiculoneuritis in puppies, usually along with some degree of accompanying meningoencephalomyelitis and myositis.
 - b. Both organisms typically cause a polyradiculoneuritis in puppies less than 3 mo of age, that is most profound in the lumbosacral nerve roots, especially ventral roots. The puppies typically experience an acute paraparesis

trigeminal nerves and/or masticatory muscles should be ruled out. In particular, multiple cranial nerve mononeuropathy due to mononuclear cell neoplasia (lymphosarcoma, myelomonocytic cancer) should be considered as a differential diagnosis, especially if clinical signs do not resolve within several weeks. Obtaining a vaccination history is important, as rabies can present with a similar clinical picture (i.e., dropped jaw). In masticatory myositis (see Chapter 13), trismus is the typical presentation, rather than a dropped jaw.

- d. This is a self-limiting disease, and most patients recover fully within 2–3 wk. Glucocorticoid therapy has been advocated early in the course of the disease, but there is little evidence of efficacy. Although glucocorticoid treatment of dogs with trigeminal neuritis is not contraindicated, such therapy may diminish subsequent responsiveness to combination chemotherapy in dogs whose trigeminal nerve dysfunction is due to mononuclear cell neoplasia. Some patients may have to be hand fed, or fed through a pharyngostomy, esophagostomy, or gastrostomy tube (i.e., those patients with dysphagia) during recovery.

9. Hemifacial spasm^{182–184}

- a. A rarely reported hyperactivity of the facial nerve in dogs and cats, this disorder probably reflects a secondary irritation of the facial nucleus and/or nerve. Potential diseases that could cause irritation include otitis media (facial nerve) or brain-stem disease (facial nucleus and/or nerve), such as neoplasia, or infectious/inflammatory disorders (e.g., GME).
- b. The affected patient typically has an asymmetric facial countenance, with the nose and lips pulled toward the affected side. A small palpebral fissure with blepharospasm, and a slightly elevated ear may also be appreciated on the affected side.
- c. Diagnosis is based upon clinical signs. This syndrome can be confused with secondary facial muscle contracture due to prior facial nerve paralysis. The treatment and prognosis depend upon the underlying cause of the hyperirritability.

F. Ischemic: Ischemic neuromyopathy^{1,4,6,108}

This is an ischemic insult due to vascular occlusion of the arterial supply to the limbs by an embolus. Both pelvic limbs are typically affected. This is usually reported in cats in association with cardiomyopathy, but has also been reported in dogs with a variety of underlying disorders. The vascular occlusion and resultant inflammatory mediators (which impair collateral circulation) result in damage to both peripheral nerves and muscles of the affected limbs. This disorder is discussed in more detail in Chapter 13.

G. Traumatic^{1,4,6,18,185–211}

- 1. Traumatic neuropathies are common in dogs and cats, and most often are a result of automobile accidents. Some of these neuropathies may be associated

with fractures. Sciatic nerve injury occurs occasionally with pelvic fracture/luxations, especially sacroiliac luxations, sacral wing, caudal acetabular, and ischial fractures. The sciatic nerve may be injured at the time of trauma, or may be progressively compressed during the bone-healing process by proliferating connective tissue. Sciatic nerve entrapment by osteophytes associated with hip dysplasia has been reported in the dog, but is considered a rare phenomenon. Radial nerve injury may occur with humeral fractures, but is extremely uncommon.

Extremity injuries may be complicated by osteofascial compartment syndrome or reflex sympathetic dystrophy, infrequent trauma-related phenomena that involve peripheral nerves. Osteofascial compartment syndrome occurs when hemorrhage and/or edema accumulate within a closed space whose borders are made up of skeletal muscle fascia or bone (osteofascial compartment). If the resultant pressure rise within the compartment is of sufficient magnitude and duration, damage to both muscle and nerve within that compartment may occur. Reflex sympathetic dystrophy is a poorly understood phenomenon, usually associated with extremity trauma, in which the affected limb becomes very painful and exhibits various autonomic abnormalities (e.g., edema, increase or decrease in temperature, sweating). This syndrome typically occurs weeks after the traumatic event in people and is thought to be mediated by the sympathetic nervous system. Reflex sympathetic dystrophy has been reported in the dog.

Most traumatic neuropathies are traction injuries, with no evidence of orthopedic problems (e.g., brachial plexus avulsion). Brachial plexus injury is commonly encountered in dogs and cats, and is thought to be caused by severe abduction and/or traction of the thoracic limb. These injuries may be partial or complete. Avulsion of the nerve roots appears to be a common form of brachial plexus injury, perhaps due to the lack of a perineurium over the nerve roots. The avulsions are typically intradural, in close proximity to the spinal cord. Ipsilateral Horner's syndrome and lack of a cutaneous trunci reflex often accompany brachial plexus avulsions, because of damage to the T1–T3 and C8–T1 roots, respectively. Other causes of traumatic neuropathies include missile injuries (e.g., gunshot wounds), bite wounds, and iatrogenic causes (e.g., inadvertent surgical trauma, injection injuries to the sciatic nerve). There are three general classes of peripheral nerve injury. From least severe to most severe, these are:

- a. Class 1 (Neurapraxia)—this refers to a transient lack of nerve function, with little or no structural damage to the axons or their supportive connective tissue structures. This temporary dysfunction may be due to ischemia (no structural damage) and/or mild paranodal demyelination. The degree of motor and proprioceptive dysfunction is variable, but nociceptive function is preserved for the most part (large-diameter axons are preferentially affected). Spontaneous recovery is expected within days to a

month, depending upon the degree of demyelination. Neurogenic muscle atrophy is unlikely, as the axons are structurally intact.

- b. Class 2 (Axonotmesis)—in this type of injury, some or all of the axons of the nerve are disrupted structurally, but the connective tissue support (e.g., Schwann cell basal lamina, endoneurium) remains intact. These axons can regrow along the connective tissue scaffold. Substantial motor, proprioceptive, and nociceptive dysfunction is expected with this type of injury, the extent of which depends on the number of axons damaged. Neurogenic muscle atrophy is likely with this class of injury.
 - c. Class 3 (Neurotmesis)—this class of injury reflects complete severance of the axons of the nerve, as well as the connective tissue support. These axons will not regrow (no guiding scaffold) without surgical intervention. Complete motor, proprioceptive, and nociceptive (i.e., no pain perception) dysfunction occurs with this class of injury. Neurogenic muscle atrophy is to be expected. Note that a severe class 2 injury may be clinically indistinguishable from a class 3 injury.
2. Localization of peripheral nerve injuries and estimation of their severity is important both for deciding on treatment options and for judging prognosis. Cutaneous sensation can be utilized as a clinical tool in localizing peripheral nerve lesions. Autonomous zones are those sensory areas of the skin supplied only by a particular nerve (e.g., dorsal aspect of the metacarpus-radial nerve). The clinician should be aware of these autonomous zones (Fig. 12.8). With brachial plexus injuries, there may be inconsistency in the patterns of sensory versus motor deficits, as the ventral nerve roots appear to be more susceptible to damage than the dorsal nerve roots. Electrodiagnostic tests can be used both for localizing purposes and for providing prognostic information in some peripheral nerve injuries. These tests should be performed a minimum of 5–7 days postinjury, as severed nerves will still conduct impulses, and denervated muscle may still be electrically silent prior to this time period.
 3. In most cases of peripheral nerve trauma, there is no specific treatment that will affect outcome. However, there are some instances (e.g., nerve anastomosis with isolated distal nerve injury, surgical repair of a fracture causing secondary nerve trauma, corrective tendon transposition or joint fusion in partial brachial plexus injuries) in which accurate estimation of the location and severity of nerve trauma may assist in choosing what therapeutic course should be taken.

The prognosis for most brachial plexus injuries is poor for functional return of the limb. The majority of brachial plexus injuries are complete avulsions. The second most common scenario is damage to the caudal area of the plexus, including the contribution to the radial nerve. Cranial plexus injuries, which carry the most favorable prognosis (preservation of weight-bearing function), are rarely encountered. There is no chance of improvement with nerve root avulsion, but there may be improvement if the roots are still intact.

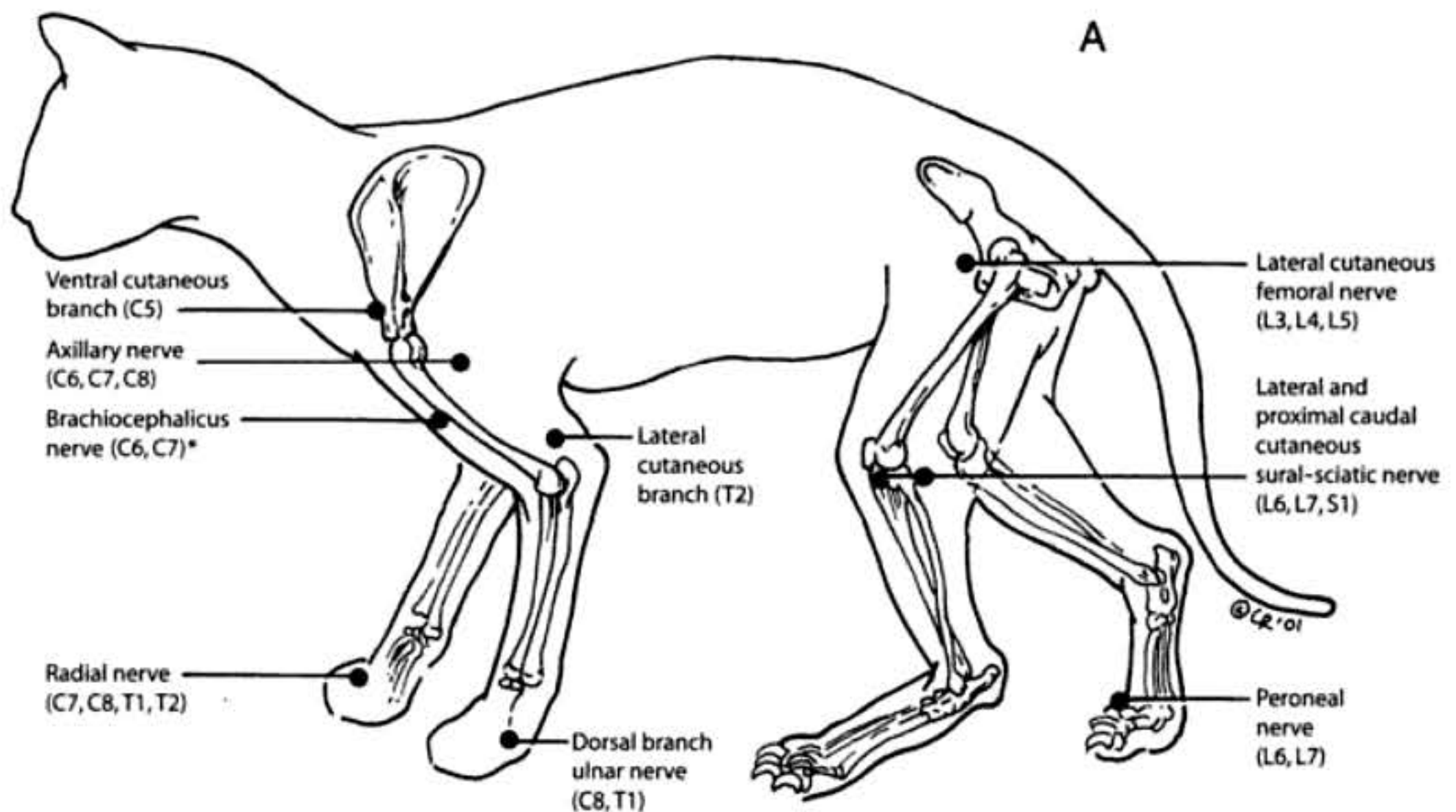


Fig. 12.8. Schematic illustration of a cat, lateral (A), ventral (B), and caudal (C) views, depicting the autonomous zones of cutaneous innervation. Differences between the cat and dog are denoted with an asterisk. There is no autonomous zone of the brachiocephalicus nerve in the cat (dog only). There is no autonomous zone for either the suprascapular or median nerves in the dog (cat only) (Illustration by Carol Rudowsky).

It may be difficult or impossible to tell in many cases whether or not the nerve injury is permanent. In one report of 30 brachial plexus injuries, only 8 dogs achieved functional limb recovery 4 mo or more following the injury. Preservation or return of triceps function is a favorable prognostic indicator for brachial plexus injuries. In general, the lack of deep pain perception to the toes is a poor prognostic indicator. Physical therapy for the affected thoracic limb and waiting several months for some return to function are indicated, before considering amputation. However, if self-mutilation due to paresthesia/dysesthesia, or severely infected abrasions (due to dragging the foot without adequate protective covering) develop within that time period, amputation may be indicated at an earlier date. The location of a class 2 or class 3 injury may also affect the prognosis. Axons regrow at a rate of 1–4 mm per day. In people, muscle motor end-plate degeneration may occur if the damaged nerve does not reestablish contact with the muscle within 18 mo. So, with a very proximal injury, the prognosis may be poor, even if axonal regeneration occurs. Despite the unfavorable outlook for functional return with most brachial plexus injuries, most dogs and cats function extremely well with three legs.

- d. Many of the earliest reported cases were euthanized due to disease severity. However, removal of contaminated food and provision of supportive therapy is likely to lead to a full neurologic recovery in the majority of affected cats.

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Chapter 13

MYOPATHIES: DISORDERS OF SKELETAL MUSCLE

Curtis W. Dewey

I. Introduction¹⁻¹¹

Skeletal muscle is the effector organ for the somatic motor nervous system. In general, clinical signs of skeletal muscle dysfunction include weakness with preservation of sensory function (e.g., nociception, proprioception), muscle atrophy, and muscle pain, or myalgia. In some diseases, muscle hypertrophy is present rather than atrophy. Also, myalgia is not a feature of some myopathies.

Skeletal muscle is composed of multinucleated cells termed myofibers that are arranged in bundles called fascicles. Each myofiber is innervated by an axonal process of a motor neuron at a specialized area of the sarcolemma (muscle cell plasma membrane) called the end plate (see Chapter 14). The myofibers contain the contractile apparatus which is comprised of interlocking myofilaments (actin, myosin, troponin, tropomyosin). Muscle contraction occurs when calcium is released from the sarcoplasmic reticulum (the myofiber endoplasmic reticulum), following sodium influx into the myofiber (depolarization). Adenosine triphosphate (ATP) is required for coordinated contraction and relaxation of the muscle fiber. A muscle enzyme called creatine kinase (CK) is required to immediately replenish ATP from adenosine diphosphate (ADP) by cleaving a high-energy phosphate group from the compound phosphocreatine, also found in the myofiber.

There are two main types of myofibers, differentiated upon the extent of histochemical staining with ATPase (muscle biopsy samples). Type I fibers are “slow-twitch” (relatively high levels of oxidative enzymes and lipid, low glycogen content) fibers and Type II fibers are “fast-twitch” (relatively high levels of glycogen, lesser amounts of oxidative enzymes and lipid) fibers. A uniquely staining fiber type is also found only in masticatory muscle, called Type IIM. One motor neuron will innervate a number of myofibers within a fascicle, and the fiber type of those myofibers will all be the same. The motor neuron and the myofibers it innervates is called a motor unit. The motor neuron dictates the fiber type of the myofibers of its motor unit. The myofibers of a single motor unit are normally scattered through a fascicle, giving a “checkerboard” appearance to the stained biopsy sample.

In some cases, it will be difficult to discern a myopathy from a neuropathy or neuromuscular junction disorder. Diagnosis of myopathies is based upon the neurologic examination findings as well as specific diagnostic tests. Typical diagnostic tests to pursue when a myopathy is suspected include serum creatine kinase measurement (elevations suggest muscle damage), electrodiagnostics (remember that electromyograph [EMG] abnormalities can be seen with neuropathies and myopathies), and muscle/nerve biopsies. In addition to the ATPase stain, there is a barrage of histochemical stains that can be applied to sections of a single muscle biopsy to help

characterize the nature of the muscle disorder. The specifics of these stains is beyond the scope of this text.

A summary of myopathies of dogs and cats is shown in Table 13.1.

II. Disorders of Skeletal Muscle in Dogs and Cats

A. Degenerative/developmental

1. Muscular dystrophy (MD)^{1-3,11-39}

- a. The term “muscular dystrophy” is often loosely applied, referring to a wide variety of inherited myopathies. In this text, this term will be used to describe those conditions associated with deficient or abnormal myofiber cytoskeletal proteins. This disorder is usually associated with either reduced levels or complete lack of a subsarcolemmal protein called dystrophin. Dystrophin is thought to have an important structural role for myofibers and may also serve a vital role in cellular homeostasis, possibly as a regulator of intracellular calcium transport. A number of dystrophin-associated proteins (e.g., sarcoglycans, dystroglycans), as well as laminins (basement membrane proteins) may also be deficient in some forms of MD.

An X-linked inherited trait, believed to be the veterinary analog of Duchenne’s and Becker’s muscular dystrophy of humans (dystrophin deficiency), has been described in various dog breeds (Golden retriever, Rottweiler, German shorthaired pointer, Irish terrier, Samoyed, Belgian Groenendaeler Shepherd, miniature Schnauzer, Rat terrier, Brittany spaniel, Japanese Spitz) and cats. Progressive muscle atrophy predominates in dogs (although some muscle groups tend to hypertrophy), whereas muscle hypertrophy is the hallmark of MD in cats. The pathologic change in affected muscle is characterized histologically by variation in myofiber size (including both degenerating and regenerating myofibers), with necrosis and mineralization of myofibers.

- b. This disease is best described in the Golden retriever. Clinical signs of partial trismus and a “bunny-hopping” gait may be appreciated as early as 6 wk of age in male puppies. Although MD is largely restricted to males, it has been reported in female dogs. Signs typically progress over 3–6 mo, after which time the disease often stabilizes. Common clinical signs include progressive muscle atrophy of the limbs (proximal limb muscles may undergo hypertrophy in some dogs), head, and trunk, exercise intolerance, stilted gait, plantigrade stance (with associated tarsal joint contracture), excessive salivation (pharyngeal dysfunction), weak bark (dysphonia), kyphosis that progresses to lordosis, and hypertrophy of the muscles of the base of the tongue. Spinal reflexes are normal initially but may become decreased due to muscle fibrosis. Inhalation pneumonia from pharyngeal/esophageal dysfunction and heart failure due to cardiomyopa-

remaining two dogs evaluated had two reportedly similarly affected siblings (not evaluated clinically). The etiology of this disease is unknown. Distal myopathy of Rottweilers appears to be similar to distal myopathy of people, a broad category of autosomally inherited myopathies that primarily affect distal appendicular muscles.

- b. The age at which the dogs were evaluated was between 4 and 7 mo, but all dogs had exhibited an abnormal gait and posture within the first several weeks of life. Characteristic clinical signs of dysfunction include a palmigrade and plantigrade stance (Fig. 13.2), splayed digits in the forelimbs (Fig. 13.3), generalized weakness, and exercise intolerance.
- c. Diagnosis is based primarily on signalment, characteristic clinical features, and abnormal muscle biopsy histopathology results. Creatine kinase levels were normal in one dog and only mildly elevated in the two others in



Fig. 13.2. Characteristic posture of a Rottweiler with distal myopathy (Courtesy of Dr. Stephen Hanson).



Fig. 13.3. Splaying of the digits, characteristic of Rottweiler distal myopathy (Courtesy of Dr. Stephen Hanson, reprinted with permission⁵²).

which it was measured. Electromyography was performed in two of the four dogs. In one dog, rare fibrillation and positive sharp waves were identified. No EMG abnormalities were identified in the other dog. Both dogs had decreased amplitude of interosseus compound muscle action potentials, elicited during motor nerve conduction velocity testing. Plasma carnitine levels were decreased in all four dogs. Muscle carnitine levels were below normal levels in three dogs, and in the low-normal range in the remaining dog. Dystrophin immunocytochemical staining was normal in the two dogs for which this test was performed.

- d. At present, the prognosis for this myopathy appears to be poor. All four dogs were euthanized, three due to the severity of the disease, and one due to an unrelated behavioral disorder. This latter dog's clinical signs appeared to improve somewhat with oral carnitine supplementation, but did not deteriorate after carnitine withdrawal. The clinical significance of low plasma and muscle carnitine levels in this disorder is unknown but is felt to be a secondary, rather than causative, phenomenon. The potential efficacy/inefficacy of carnitine supplementation for this myopathy remains to be determined.

4. Myotonia congenita^{1,3,12,13,40,55-72}

- a. This disorder is believed to be inherited as an autosomal recessive trait in Chow Chow dogs and miniature Schnauzers. Other breeds reported with a similar condition include Staffordshire terrier, Rhodesian Ridgeback, Great Dane, West Highland White terrier, Samoyed cross, and Labrador retriever. Myotonia congenita has recently been described in six domestic shorthaired kittens. The four kittens in one report were from separate litters, but the queens of those litters were related. The discerning clinical feature of this disorder is sustained muscle contraction after cessation of voluntary movement. Failure of muscle relaxation is believed to be due to abnormal sarcolemmal chloride conductance. The decreased chloride conductance leads to hyperexcitability of the muscle membrane. Subsequent accumulation of potassium ions in the T-tubule system is responsible for sustained muscle contraction following initial depolarization. Abnormal sarcolemmal chloride channels, due to an autosomally inherited genetic defect, have been demonstrated as the cause of myotonia congenita in the miniature Schnauzer. There are several forms of myotonia congenita in humans, some of which are due to abnormal sodium conductance across the sarcolemma.
- b. Clinical signs are usually appreciated when affected puppies and kittens begin to ambulate. Affected animals typically appear worse after a period of rest. Cold temperatures also tend to cause exacerbation of clinical signs. The gait is stiff and tends to improve or even normalize with activity. The pelvic limbs are often more severely affected than the thoracic limbs; in canine myotonia, they may be advanced simultaneously in a "bunny-hopping" fashion. It may be difficult for affected dogs to flex the stifle joints.

risk of anesthesia in these patients. Anesthesia may be both difficult and dangerous due to stenosis of the laryngeal glottis. Also, people with myotonia are predisposed to anesthetic-induced malignant hyperthermia. The characteristic finding on EMG is bizarre high-frequency discharges that wax and wane. These discharges are frequently referred to as “dive-bombers,” due to their waxing and waning nature. Others have likened their sound to a motorcycle engine.

- d. There is some evidence that using membrane-stabilizing agents may be helpful in relieving clinical signs in myotonic dogs. Procainamide is thought to be more effective than phenytoin or quinidine. Other drugs that have been used to treat myotonia in dogs include carbamazepine, tocainide, nifedipine, and mexiletine hydrochloride. Environmental modification alone is recommended to control clinical signs in myotonic cats. These kittens tend to be well managed without drug therapy, and drugs typically used to control canine myotonia have unacceptable toxicity risks in cats. Myotonia congenita is not considered a progressive disease, and clinical signs of dysfunction tend to stabilize between 6–12 mo of age. In general, most dogs and cats with myotonia congenita are not severely disabled, and therefore the prognosis for long-term survival is favorable. The prognosis for sustained improvement of clinical signs of myotonia is guarded, however.
5. Fibrotic myopathy (gracilis/semitendinosus myopathy)^{12,73–78}
 - a. This is an idiopathic disorder characterized by replacement of muscle tissue with dense fibrous connective tissue. It occurs most commonly in dogs, especially adult male German Shepherd dogs (approximately 81% of reported cases). Other breeds reported with fibrotic myopathy include Belgian Shepherd, Boxer, Old English sheepdog, Doberman Pinscher, Saint Bernard, and Bobtail. It has been reported in one cat. The gracilis muscle is most often affected (86% of cases), but the semitendinosus muscle may also be affected either alone or concurrently. Involvement of the supraspinatus and quadriceps muscles have been reported, but this is rare. The fibrotic gracilis/semitendinosus muscle produces a tethering effect, interfering with coxofemoral joint abduction, as well as stifle and hock joint extension. The pathogenesis is unknown. Autoimmune myopathy, neuropathy, isolated muscle trauma, repeated microtrauma, and vascular compromise have all been suggested as possible etiologies.
 - b. Age of onset of dysfunction ranges from 8 mo to 9 yr (mean, 5 yr). Clinical signs are usually limited to an apparently nonpainful pelvic limb lameness, which is more obvious at a trot than at a walk. In most cases, the lameness has an insidious onset and progresses over weeks to months before reaching a plateau. Occasionally, acute onset of lameness is reported. Bilateral involvement occurs in approximately 26% of cases. When both pelvic limbs are affected, the degree of dysfunction may not

be symmetric; also, one limb may be affected initially, the other becoming dysfunctional at a later date. Although classically considered a nonpainful disorder, one study found that a painful response could be elicited from the majority of affected dogs with hip abduction and/or digital pressure applied to the distal aspect of the fibrotic muscle. The fibrous muscle prevents full extension of the pelvic limb during ambulation. The lameness in the affected limb is characterized by internal rotation of the stifle and external rotation of the hock as the limb is advanced (Fig. 13.5). The foot performs a “flipping” motion at the end of each stride. The resultant gait is often described as “jerky” or “goose stepping.” Affected muscle tissue may be visibly abnormal and the distal myotendinous area is often firm and hypertrophied when palpated (Fig. 13.6).

- c. Diagnosis is based primarily upon signalment and characteristic clinical findings. Increased thickness may be appreciated in affected muscles with both radiographs and ultrasonography. Creatine kinase values are typically normal or slightly elevated. Electromyography often fails to record any abnormal electrical activity. There are reports of both increased EMG activity and lack of normal insertional activity. Muscle biopsy reveals dense collagenous connective tissue.
- d. Medical therapies for fibrotic myopathy (e.g., corticosteroids, penicillamine, colchicine) have been ineffective. Various surgical procedures (e.g., tenotomy, Z-plasty, excision of affected muscle) have met with poor



Fig. 13.5. Typical pelvic limb gait of a dog with fibrotic myopathy (From: Lewis DD, Parker RB, Bloomberg MS (eds), *Self Assessment Colour Review of Small Animal Orthopaedics*. London, Manson Publishing Ltd, 1998. Reprinted with permission).



Fig. 13.6. Bilateral fibrosis of the gracilis muscles in a dog with fibrotic myopathy (From: Lewis DD, Parker RB, Bloomberg MS (eds), *Self Assessment Colour Review of Small Animal Orthopaedics*. London, Manson Publishing Ltd, 1998. Reprinted with permission).

long-term success. Improvement in gait postsurgery is often substantial but transient, lasting only a few months. If the abnormal gait is not severely limiting the patient's lifestyle, no treatment is recommended.

6. Nemaline myopathy⁷⁹⁻⁸²

- a. Nemaline myopathy is a rare, presumably inherited disorder described in young related cats. Congenital nemaline myopathy has also been reported in two dogs, a 10-mo-old Border collie, and an 11-yr-old Schipperke. Nemaline rods were also observed in muscle biopsy specimens from a dog with hyperadrenocorticoid myopathy and a dog with hypothyroid myopathy. Structures characteristic of nemaline rods were observed in muscle fibers of a 6-mo-old Great Dane that had a myopathy with corelike structures. This dog was thought to have been affected by a myopathy similar to central-core myopathy of people. Central core myopathies are a rare and poorly understood group of congenital myopathies. Finally, nemaline rods have been reported as incidental findings in muscle biopsies of dogs with neuromuscular disease. The presence of nemaline rods in a muscle biopsy is not necessarily specific for nemaline myopathy.

A diagnosis of nemaline myopathy should be suspected when there are numerous nemaline rods present in the absence of any other cause for a myopathy. The pathogenesis of nemaline myopathy is unknown, but special stains of muscle biopsy specimens reveal rod-shaped inclusions within myofibers (nemaline rods). In human nemaline myopathy, these rods have been shown to be composed of cytoskeletal proteins identical to those found in the Z-band area of the contractile filament apparatus. A myofiber cytoskeletal protein abnormality is suspected.

- b. The reported cats had an acute onset of clinical signs between 6 and 18 mo of age. Clinical signs included weakness, a rapid and crouched hypermetric gait, muscle tremors, hyporeflexia, muscle atrophy, and reluctance to move. Only the muscle atrophy appeared to be progressive. Both congenital canine nemaline myopathy cases had slowly progressive clinical signs that included exercise intolerance, and reluctance to stand and walk. The Border Collie displayed tremors in all limbs, muscle atrophy, and absence of patellar reflexes. Additional clinical signs of dysfunction in the Schipperke included a stiff gait, spontaneous limb jerking, and decreased withdrawal reflexes in all four limbs. The single case of myopathy with corelike structures had generalized muscle weakness that worsened with exercise. The endocrine myopathy cases had clinical signs of dysfunction typical for their respective myopathic disorders.
 - c. Diagnosis is based upon signalment, clinical signs, and demonstration of nemaline rods on muscle biopsy samples. Creatine kinase levels were only mildly elevated in the reported cats and electromyography (EMG) evaluation was normal. Similarly, the creatine kinase level of one of the congenital canine cases was normal, the other slightly elevated. EMG changes in these two dogs were mild. Muscle biopsy from the Great Dane with corelike myopathy revealed sharply defined, pale pink inclusions (central cores) that occupied 20%–80% of the muscle fiber volume in approximately half of the muscle fibers.
 - d. Although only the muscle atrophy was progressive, the reported cats continued to lose condition and became inappetent. All the cats were eventually euthanized. The disorder in the reported dogs was slowly progressive over several years. Clinical signs in the Great Dane with central-core myopathy persisted, and the dog was euthanized at 18 mo of age. There is no known treatment for nemaline myopathy and the prognosis for recovery is poor.
7. Dancing Doberman disease
- This is a recently described idiopathic syndrome in adult Doberman Pinschers that has characteristics of both a neuropathy and a myopathy. It is discussed in more detail in Chapter 12.
8. Myositis ossificans (fibrodysplasia ossificans progressiva)^{73,82}
- a. This is a rare idiopathic disorder of dogs and cats in which proliferation of fibrovascular tissue within muscle occurs, with secondary calcification and ossification. It is not known if this disease represents a primary muscle disorder or if this is an abnormality of connective tissue adjacent to muscle (e.g., tendons, fascia) that leads to a secondary myopathy.
 - b. This disorder typically affects young adult to middle-aged animals of both sexes. Clinical signs include progressive weakness and stiffness of gait, enlargement of proximal limb muscles, and myalgia. Focal, firm swellings may be evident on muscle palpation.
 - c. Diagnosis is based primarily upon signalment, clinical signs, and radiographic evidence of mineralized/ossified densities (usually multiple)

within muscle tissue. Creatine kinase levels are typically elevated, and EMG evaluation reveals abnormal potentials. Histopathologically, fibrosis, myofiber necrosis and phagocytosis, and areas of calcification/ossification may be seen.

- d. Since this tends to be a progressive disease, the prognosis is considered guarded to poor. However, focal lesions may regress or respond favorably to surgical excision.
9. Pharyngeal/esophageal dysfunction of Bouviers^{83,84}
 - a. A myopathy primarily affecting pharyngeal and esophageal musculature has been described in 24 Bouvier des Flandres dogs from the Netherlands. The pathogenesis of this disorder is unknown, but muscle histopathology revealed abnormalities similar to those observed in dystrophin-related muscular dystrophy (DRMD). It has been suggested that this disorder may be the canine analog of oculopharyngeal muscular dystrophy of people. Although suspected to be a heritable trait, the mode of transmission is unknown. Four adult female Bouviers with generalized muscle weakness and megaesophagus were described in the United States. These dogs also had histopathologic changes on muscle biopsies consistent with DRMD. It is unknown whether these dogs had a variation of the same disorder as the group in the Netherlands.
 - b. Both males and females were affected, with an age range of presentation from 6 mo to 9 yr of age. The predominant clinical sign of dysfunction was dysphagia. Seven of the 24 dogs with dysphagia also exhibited regurgitation. Regurgitation was the predominant clinical feature in 3 dogs.
 - c. Tentative diagnosis of this myopathy was based upon historical and clinical signs, as well as abnormal pharyngeal and esophageal movement on fluoroscopic examination. Only 7 dogs had radiographically obvious air accumulation in the esophagus. In 20 dogs in which serum creatine kinase levels were evaluated, 7 dogs had normal values, and creatine kinase levels were elevated in 13 dogs. EMG abnormalities of the pharyngeal and/or esophageal musculature were found in all but 1 dog examined. Histopathologic evaluation of pharyngeal/esophageal muscles from affected dogs revealed changes characteristic of DRMD. In 2 dogs, these characteristic abnormalities were also apparent in temporalis, masseter, and laryngeal musculature.
 - d. There is no known effective treatment for this disorder. Four dogs with dysphagia underwent cricopharyngeal myotomy. One of these dogs improved, but the other 3 died of aspiration pneumonia within two days of surgery. The majority of the affected dogs were euthanized due to continued dysphagia. The prognosis for dogs with this disorder appears to be poor.
 10. Polysystemic disorder of English Springer spaniels⁸⁵
 - a. Three related young English Springer spaniels have been described with the combination of polymyopathy, dyserythropoiesis, and cardiac abnormalities. The etiology of this polysystemic disorder is unknown, but is suspected to be a heritable variant of muscular dystrophy.

- b. All three dogs developed clinical signs of dysfunction within the first 6 mo of life, and all were considered small for their age. One dog occasionally regurgitated, and the other two had decreased gag reflexes. Slowly progressive temporal muscle atrophy developed in all dogs, with subsequent partial trismus. To a lesser degree, pelvic limb muscle atrophy occurred over time. One dog exhibited a stiff gait, most notable in the pelvic limbs, often bunny hopping when ambulating. Exercise intolerance was not a notable feature in any of the three dogs.
 - c. Diagnosis of this disorder was based upon both antemortem and necropsy evidence of concurrent polymyopathy, dyserythropoietic anemia (erythrocytes with abnormal morphology, including blast forms), and various cardiac abnormalities (e.g., right ventricular enlargement, enlargement of conus arteriosus, ascending aorta enlargement, ventricular premature complexes). Varying degrees of megaesophagus and abnormal esophageal motility were evident on thoracic radiographs and fluoroscopic evaluation, respectively. Serum creatine kinase levels were normal in one dog, and slightly elevated in another. EMG abnormalities were not evident in the one dog in which electrodiagnostics were pursued. Abnormal muscle pathology in affected dogs included marked fiber size variation and fiber splitting.
 - d. There is no known effective therapy for this disorder and the prognosis for recovery is poor. All three dogs were euthanized.
11. Cricopharyngeal achalasia⁸⁶⁻⁹³
- a. This is an uncommon and enigmatic disorder of young dogs. It is characterized by failure of relaxation of the cricopharyngeus muscle during the oropharyngeal phase of swallowing. The underlying reason for the lack of cricopharyngeus relaxation is unknown. Suggested etiologies include myopathy, neuropathy (affecting glossopharyngeal nerve and pharyngeal branch of the vagus nerve), junctionopathy, and central nervous system (brain stem) lesion.
 - b. Numerous dog breeds have been reported with cricopharyngeal achalasia. Spaniel breeds appear to be overrepresented in the literature; there is one report of cricopharyngeal achalasia occurring in Cocker spaniel littermates. Clinical signs of dysfunction are usually evident at the time of weaning and remain static, unless aspiration pneumonia develops. Dysphagia is the hallmark clinical sign of dysfunction. Other characteristic clinical signs include regurgitation (typically immediately following attempted swallowing), nasal reflux of ingested food, coughing, and either weight loss or failure to gain weight. Dogs with this disorder may be more able to swallow liquids than solids, but ingesting liquids may lead to more nasal reflux than solids.
 - c. The diagnosis of cricopharyngeal achalasia is based primarily upon history, signalment, and characteristic clinical features, as well as ruling out other causes of dysphagia and regurgitation (e.g., idiopathic megaesopha-

gus, myasthenia gravis, vascular ring anomalies). Radiographs of the pharyngeal area and thorax should be obtained to rule out pharyngeal foreign bodies and megaesophagus, respectively. Also, the presence or absence of aspiration pneumonia can be ascertained by thoracic radiographs. Crucial to diagnosis is evaluation of swallowing using contrast fluoroscopy (Fig. 13.7). This radiographic evaluation should confirm failure of cricopharyngeal relaxation during the swallowing reflex. Endoscopic evaluation of the pharyngeal area will be normal, and there is typically no appreciable impediment to passing the scope through the pharyngeal region.

- d. The treatment for cricopharyngeal achalasia is myotomy or myectomy of the cricopharyngeus muscle. This surgical therapy is highly effective for this disorder. However, if the diagnosis is incorrect, cricopharyngeal myotomy/myectomy may not only be of no therapeutic value, but may lead to life-threatening aspiration pneumonia.

12. Episodic muscle hypertonicity ("cramp")⁹⁴⁻¹⁰⁶

- a. This rare disorder, reported most frequently in the Scottish terrier breed ("scotty cramp"), is characterized by episodic muscle hypertonicity. The episodes are of variable frequency and severity and are induced by stress, exercise, and excitement. The disease appears to be inherited as an autosomal recessive trait in Scottish terriers. Although the pathogenesis is not completely understood, clinical manifestations of this disorder appear to be due to a functional deficiency of serotonin in the central nervous system. Drugs that potentiate CNS serotonergic effects (e.g., acepromazine) alleviate clinical signs, whereas those that decrease CNS serotonergic effects (e.g., amphetamine) either worsen or induce clinical signs. A similar, if not identical, condition has been described in Dalmatians, Cavalier King Charles spaniels, and Norwich terriers. In the report concerning the affected Dalmatians, a similar condition was mentioned in a Cocker spaniel and a Wire-haired terrier. It has been suggested that this group of disorders may represent a form of dyskinesia (see Chapter 6).
- b. The majority of affected dogs initially exhibit clinical signs of dysfunction within the first year of life, usually between 2 and 6 mo of age. An age range of 6 wk to 3 yr has been reported for Scottish terriers, and 14 wk to 4 yr for Cavalier King Charles spaniels. The two affected Dalmatians were 4 and 8 mo old. Affected dogs are normal between episodes. Episodes of muscle cramping are usually elicited by exercise, but can also be associated with other forms of stress or excitation. The extent of muscle hypertonicity may vary from primarily pelvic limb involvement to severe hyperflexion of all limbs with subsequent collapse. Pelvic limb hypertonicity is typically noticed first during an episode. Affected dogs often exhibit exaggerated flexion action of the pelvic limbs, referred to occasionally as a "string-halt" or "goose-stepping" gait. Some dogs will advance the pelvic limbs simultaneously in a bunny-hopping fashion. If signs progress, the lumbar spine may become arched, and the thoracic limbs may become

last for approximately 10 min. Recovery is often hastened with rest or removal of the inciting stressful stimulus. Hypertonic episodes do not appear to increase in frequency or intensity over time.

- c. Diagnosis of this disorder is based on the following: (1) typical signalment, historical, and clinical features; (2) ability to induce a hypertonic episode with intramuscular amphetamine (0.5–2.0 mg/kg IM); and (3) ability to cause remission of a hypertonic episode with diazepam (0.5–1 mg/kg IV), acepromazine (0.075–0.1 mg/kg IM), or chlorpromazine (1.0–1.75 mg/kg IM). Basic bloodwork and creatine kinase values are normal, as are EMG studies. Muscle biopsy results are also generally normal. In one report on Cavalier King Charles spaniels, fairly nonspecific ultrastructural muscle fiber abnormalities were described, of questionable clinical significance.
- d. Treatment for episodic muscle hypertonicity is typically either with oral diazepam or an oral promazine drug (e.g., acepromazine). Cavalier King Charles spaniels tend to be less responsive to diazepam than other breeds with the condition. Other therapies reported to decrease frequency and severity of episodes include Vitamin E and tryptophan. This is a nonprogressive disorder that tends to improve with therapy. Life spans of affected dogs do not appear to be shortened by the disease.

B. Metabolic

1. Hypokalemic myopathy^{2,3,11–13,107–114}

- a. A relatively common myopathy associated with low extracellular potassium levels is encountered in cats. Most of these cats have chronic renal dysfunction with subsequent potassium loss through the urine. Other conditions associated with hypokalemic myopathy in cats include hyperthyroidism, dietary potassium deficiency, hyperaldosteronism, fluid overadministration, chronic vomiting/diarrhea, and overuse of potassium-wasting diuretics. There is also a suspected hereditary condition of unknown pathogenesis in Burmese kittens with periodic hypokalemia and signs of myopathy. This condition is suspected to be inherited as an autosomal recessive trait. It may be similar to hypokalemic periodic paralysis of people. Hypokalemia leads to hyperpolarization of the sarcolemma resting membrane potential, making it refractory to depolarization and subsequent contraction.
- b. Most cats with this condition are older and have evidence of renal dysfunction. The Burmese kittens with intermittent hypokalemia and myopathy ranged between 2 and 6 mo of age. Clinical signs are typically acute in onset and include neck ventroflexion, myalgia, reluctance to ambulate, and a stiff, stilted gait. With severe hypokalemia, respiratory paralysis and rhabdomyolysis can occur.
- c. Diagnosis is based upon signalment, historical and clinical findings, as well as supportive evidence of a myopathy in a cat with hypokalemia. The

potassium level in affected cats is less than 3.5 mEq/L, and often is less than 3.0 mEq/L. Creatine kinase levels are usually moderately to markedly elevated. Electromyographic (EMG) evaluation typically reveals abnormal activity such as fibrillation potentials, positive sharp waves, and bizarre high-frequency potentials. Muscle biopsy samples often reveal no or very mild abnormalities. Resolution of clinical signs with potassium supplementation also supports the diagnosis.

- d. Treatment of this condition is oral potassium gluconate at an initial dose of 5–8 mEq/kg/day, divided into two doses. Normal potassium levels are often achieved within 1–3 days with this therapy. Maintenance therapy of 2–4 mEq/day is usually sufficient after achieving normal serum potassium levels. Potassium administration via intravenous fluids is usually counterproductive, because the dilutional and diuretic aspects of fluid administration actually further lower the potassium level.

In life-threatening hypokalemia, concentrated intravenous potassium solutions can be administered at a rate of 0.4 mEq/kg/hour. However, this is potentially dangerous and can lead to fatal cardiac arrhythmias without close monitoring of the serum potassium level and the electrocardiogram. An alternative is a dopamine infusion of 0.5 µg/kg/minute. This may cause a transient increase in serum potassium, and allow time for oral potassium supplementation. The prognosis for this condition with proper therapy is generally favorable. Most cats exhibit obvious improvement within 1–3 days of potassium supplementation, although complete recovery may take several weeks.

2. Hyperkalemic periodic paralysis^{12,114–116}
 - a. Hyperkalemic periodic paralysis (HPP) is an uncommon autosomal dominant genetic disease in people that has been reported in one dog. The clinical hallmark of HPP is episodic flaccid muscle weakness, which often leads to transient (usually less than 1 hr) paralysis. The episodes are typically induced by exercise and exposure to cold environmental temperatures. Part of the clinical definition of HPP is exacerbation of clinical signs following oral potassium administration. The physiologic mechanisms involved in this disorder are not well understood, but are thought to involve either excessive release of potassium from the myofiber across the sarcolemma, and/or increased passive motion of sodium across the sarcolemma into the sarcoplasm. Abnormal glucose metabolism has also been implicated as a contributor to fluctuating serum potassium levels in patients with HPP. The weakness is thought to be due to muscle release of potassium ions, rather than a response of muscle to high serum levels of potassium. Although episodes are typically associated with elevated serum potassium levels, this is not always demonstrable. Also, the elevated serum potassium levels are increased as compared to precollapse levels, but are often still within the normal range.

- b. In people with HPP, clinical signs of dysfunction initially occur in infancy or early childhood. The one reported case in a dog occurred in a 7-mo-old female Pit bull. The dog began collapsing approximately once a day, usually coincident with playing. Weakness typically began with the pelvic limbs and would quickly progress to involve the thoracic limbs. The dog's neck became limp, her tongue would protrude, and she would collapse. The episodes lasted approximately 10–15 sec. After 3 mo, the episodes had increased in frequency to several times a day. There was no impairment of consciousness during the episodes.
 - c. Diagnosis of HPP is supported primarily by demonstrating an exacerbation of clinical signs following oral potassium administration, as well as a positive response to therapy. Sustained elevation of serum potassium levels associated with collapsing episodes also supports a diagnosis of HPP. There may or may not be EMG abnormalities in HPP patients, and creatine kinase levels are typically normal to slightly elevated. Muscle biopsy results are normal in HPP. In the reported dog, a few fibrillation potentials were documented in the lumbar musculature, and the creatine kinase was slightly elevated at one time, normal at another. A muscle biopsy revealed no abnormalities. A sustained elevation of serum potassium was demonstrated after a brief period of exercise, although this level remained within reference range. The dog experienced marked worsening of clinical signs following oral potassium administration on two separate occasions.
 - d. Treatment with acetazolamide in people with HPP is very effective, usually leading to cessation of collapsing episodes within 24 hours of treatment initiation. Acetazolamide is thought to stimulate release of both insulin and glucagon, which subsequently promotes the movement of potassium ions into muscle cells. Other therapies reportedly used in human HPP include mineralocorticoids, salbutamol, and thiazide drugs. There is some evidence that glucocorticoids may worsen collapse episodes in HPP. Administration of carbohydrates may reduce episode severity. The dog with HPP was treated with oral acetazolamide and no further collapsing episodes occurred.
3. Hyperadrenocorticism (Cushing's) myopathy^{2,3,19,114,117–120}
- a. Excessive circulating glucocorticoid levels, whether due to endogenous production or exogenous administration of glucocorticoids, can lead to a myopathy in dogs and cats. The physiologic mechanism(s) behind the development of the myopathy is(are) unknown. There is some evidence that elevated plasma glucocorticoid levels may interfere with muscle fiber mitochondrial function. Type II fiber atrophy is a consistent histopathologic feature of this myopathy.
 - b. Most dogs with naturally occurring hyperadrenocorticism are middle-aged, small-breed dogs. Clinical signs of glucocorticoid excess (polyuria/polydipsia, polyphagia, pendulous abdomen) are typically noted

- prior to clinical signs of myopathy. A stiff, stilted gait (especially in the pelvic limbs), weakness, and muscle atrophy may be apparent with hyperadrenocorticoid myopathy. Both clinical signs and diagnostic test results may be consistent with myotonia, hence the terms "Cushing's myotonia" and "pseudomyotonia."
- c. Diagnosis is based upon clinical signs of a myopathy in a patient with hyperadrenocorticism, as well as upon specific diagnostic tests. Subclinical myopathy has also been documented in dogs with hyperadrenocorticism. Other abnormalities supporting the diagnosis may include elevated creatine kinase levels, abnormal discharges on EMG examination (sometimes including waxing and waning "dive-bomber" potentials and other bizarre high-frequency discharges), and both Type I and Type II fiber atrophy (Type II atrophy may predominate) apparent on muscle biopsy samples. Accumulation of intramyofiber lipid droplets and "ragged red fibers" (see lipid storage and mitochondrial myopathies below) has also been reported in cases of hyperadrenocorticoid myopathy.
 - d. Treatment of this myopathy depends upon correcting the underlying problem causing the hyperadrenocorticism (e.g., mitotane treatment for pituitary dependent hyperadrenocorticism, discontinuing oral prednisone therapy with iatrogenic hyperadrenocorticism). The prognosis for resolution of the myopathy after correcting the underlying disorder is guarded to good.
4. Hypothyroid myopathy^{2,3,114,117,118,121-123}
- a. There is evidence in people as well as dogs that hypothyroidism may cause a myopathy. The pathogenesis is unknown. Potential mechanisms include abnormal carbohydrate metabolism, abnormal myofiber mitochondrial activity, problems with triglyceride turnover, and deranged cation transfer across the sarcolemma. On muscle biopsy, Type II fiber atrophy predominates.
 - b. The best documented cases of hypothyroid myopathy in dogs were subclinical. However, the lethargy and intolerance to exercise exhibited by some hypothyroid dogs may be due in part to myopathic changes. The clinician should bear in mind that hypothyroid neuropathy may produce similar nonspecific signs of weakness.
 - c. Diagnosis of this condition may be difficult (see Hypothyroid neuropathy, Chapter 12). An abnormal TSH response test supports the diagnosis of hypothyroidism. Creatine kinase levels may be elevated and EMG examination may reveal abnormal muscle activity. Muscle biopsy may reveal preferential Type II fiber atrophy. Similar to hypothyroid neuropathy, resolution of clinical signs with thyroid supplementation should support the diagnosis.
 - d. The prognosis for recovery is unknown, due to the absence of well-documented clinical cases.

5. Malignant hyperthermia^{114,124-141}

- a. This is a potentially life-threatening disorder described primarily in dogs, but also in cats. The human disorder is very similar to the canine disease. There is some evidence in dogs that malignant hyperthermia may be inherited as an autosomal dominant trait. The underlying disorder is abnormal calcium (Ca^{++}) release channels in the sarcoplasmic reticulum of myofibers. Sustained calcium release causes sustained muscle contraction with subsequent elevations in body temperature. Although symptoms vary in both severity and the rate of onset, severe and progressive hyperthermia (exceeding 107°F) with accompanying acidosis and hypoxia can sometimes rapidly lead to death without prompt and aggressive therapy. The most common trigger for hyperthermic episodes appears to be certain anesthetic drugs (halothane, succinylcholine, lidocaine). In some patients, excitement, stress, or exercise can induce hyperthermic episodes. Finally, a recent report suggests that the ingestion of hops from home-brewing kits can induce malignant hyperthermia episodes in dogs.
- b. Unfortunately, clinical signs may not be apparent until a life-threatening hyperthermic episode is triggered. However, susceptible dogs may have hyperactive temperaments, hypertrophic-appearing muscles, and high normal to slightly elevated resting rectal temperatures. Some of these patients may also have mild elevations of serum creatine kinase levels. Clinical signs of a hyperthermic episode can occur within minutes to a few hours after a triggering event and may include tachypnea, tachycardia, elevated temperature, limb muscle rigidity, and myoglobinuria. Severe metabolic acidosis can develop rapidly. Creatine kinase levels may also be increased. Respiratory and cardiac arrest may occur quickly, especially if appropriate therapy is not instituted immediately. In anesthetized patients, increased CO_2 production appears to be the earliest indication of a hyperthermic episode, so capnography is recommended in suspect patients. Some dogs with the exercise-induced form of the disease may have a history of intolerance to mild to moderate exercise with clinical signs of muscle weakness of varying severity.
- c. Definitive diagnosis of malignant hyperthermia can be attained with in-vitro caffeine- or halothane-contraction tests, using muscle biopsy tissue from a suspect patient. The muscle sample is exposed to a level of caffeine or halothane that will not cause muscle contraction in a normal animal. A contraction response by the muscle tissue supports a diagnosis of malignant hyperthermia. Histopathologic changes in muscle biopsy samples tend to be either inapparent or mild and nonspecific. A tentative diagnosis is based upon observing a hyperthermic episode associated with a known triggering incident. When confronted with an exercise-intolerant animal in which malignant hyperthermia is suspected, the clinician must be extremely cautious when attempting to reproduce the reported symptoms

- d. Information concerning treatment and prognosis is scant, although there is anecdotal evidence that dogs with lipid storage and mitochondrial myopathies may respond to various treatments. Some patients with carnitine deficiency will show a clinical response to oral L-carnitine supplementation (50 mg/kg, q 12 hr). Oral supplementation with riboflavin (50–100 mg per day), vitamin C (50 mg/kg per day), and coenzyme Q (1 mg/kg/day) have been recommended for people with mitochondrial myopathies, but the efficacy of these treatments is questionable. There is recent evidence in people with mitochondrial myopathies that creatine monohydrate may be beneficial. Finally, dietary management, including a low-fat, high-carbohydrate, high-protein diet, supplemented with medium-chain triglycerides may provide some benefit by bypassing the nonfunctional pathway(s) in some of these disorders.
- 8. Glycogen storage disorders (glycogenoses)^{2,3,13,40,161–165}
 - a. This is a group of rare inborn errors of metabolism in which an enzyme necessary for the synthesis or degradation of glycogen is deficient. Histopathologically, vacuolated myofibers are often observed, the vacuoles being filled with glycogen.
 - b. Clinical signs of glycogen storage diseases usually develop in the first year of life and typically include progressive muscular weakness (often exercise related), muscle atrophy, and poor growth, as compared to normal littermates. Some patients may have megaesophagus with resultant regurgitation and aspiration pneumonia, and some may have cardiac abnormalities. The glycogen storage diseases reported in dogs and cats include the following:
 - (1) Glycogenosis Type II (acid maltase or α -1, 4-glucosidase deficiency)—described in Lapland dogs.
 - (2) Glycogenosis Type III (amylo-1,6-glucosidase deficiency)—described in German Shepherd and Akita dogs. Progressive hepatomegaly is an additional clinical feature in these dogs.
 - (3) Glycogenosis Type IV (α -1,4-D-glucan deficiency)—described in Norwegian Forest cats.
 - (4) Glycogenosis Type VII (phosphofructokinase deficiency)—reported in English Springer spaniel dogs. These dogs rarely exhibit clinical signs of myopathy. They usually exhibit compensated intermittent hemolytic anemia and hemoglobinuria, due to defective erythrocytes. This has also been reported in an American Cocker spaniel dog. A syndrome of dyserythropoiesis, myopathy, and cardiac dysfunction has been described in related English Springer spaniel dogs. However, this is not thought to represent a glycogen storage disease, but rather a defect in DNA synthesis and replication.
 - c. Definitive diagnosis requires demonstrating deficient enzymatic activity for the enzyme of interest (e.g., leukocyte assay). Other supportive evidence

includes clinical signs of myopathy in a young dog or cat of a suspect breed, abnormal creatine kinase levels and/or EMG activity, and evidence of myofiber glycogen accumulation on muscle biopsy.

- d. There are no effective treatments for these diseases and most patients are euthanized due to progressive debilitation within the first one to two years of life.

C. Inflammatory/infectious

1. Masticatory myositis^{1-3,12,19,114,166-175}

- a. This is an autoimmune disorder in which antibodies are directed against the muscles of mastication (e.g., temporalis, masseter, pterygoid muscles). The pathogenesis of this disease is uncertain, but the distinct myosin isoform and myofiber type (Type II M) of masticatory muscles may explain why they are preferentially targeted by the immune response. These Type II M myofibers have a different embryologic origin (branchial arch mesoderm) than appendicular myofibers (paraxial mesoderm), and are believed to be antigenically distinct from these latter fiber types.
- b. Dogs of numerous breeds (usually large breeds) and both sexes have been reported with this disorder, but the German Shepherd dog seems to particularly predisposed. Most dogs with masticatory myositis are young adults. Cats are rarely reported with this disorder. Clinical signs typically include painful swelling of the masticatory muscles and varying degrees of trismus. Clinical signs are often acute in onset and may be recurrent. Exophthalmos and fever are also occasionally observed. Palpation of the masticatory muscles and attempts to force the jaws open often elicit a painful response. Some dogs have a history of chronic masticatory muscle atrophy without obvious painful swelling. These dogs may represent a more chronic form of masticatory myositis, neurogenic atrophy from trigeminal neuritis, or a distinct atrophic myopathy of masticatory muscles.
- c. Diagnosis of masticatory myositis is attained by demonstrating antibody localization to Type II M myofibers with the immunoreagent Staphylococcal protein A conjugated to horseradish peroxidase (SPA-HRPO). This can be done using frozen sections of the patient's temporalis muscle, or incubating the patient's serum with normal stored frozen canine muscle and the immunoreagent. Creatine kinase levels may also be elevated and EMG examination often reveals abnormalities. Muscle biopsies may reveal varying degrees of inflammatory infiltrates, and myofiber necrosis and phagocytosis.
- d. Treatment is immunosuppressive doses of prednisone (1–2 mg/kg per os, q 12 hr) for 3–4 wk, after which the dosage is tapered to every other day. Tapering is slowly continued in order to achieve the lowest every-other-day dosage that will control clinical signs. Most dogs will show a favorable response to therapy, but relapses are common. In some cases, prednisone can be replaced by azathioprine as the maintenance immunosuppressant

drug, relieving some or all of the side effects associated with glucocorticoid therapy. In general, the prognosis for this disease is favorable.

2. Extraocular myositis^{11,176,177}

- a. An inflammatory myositis restricted to the extraocular muscles has been reported in ten young dogs. The pathogenesis is unknown, but may involve an autoimmune reaction to antigenically distinct muscle fibers unique to extraocular muscles, similar to the situation in masticatory myositis.
- b. The reported dogs were between 6 mo and 3 yr of age, and included six females and four males. Six of the ten dogs were Golden retrievers. Other breeds included a German Shepherd dog, a Doberman Pinscher, a Bull Mastiff, and a mixed-breed dog. The predominant clinical sign was bilateral exophthalmos of acute onset (Fig. 13.8). One dog exhibited unilateral exophthalmos. Visual deficits and increased intraocular pressures were noted in one dog.
- c. Diagnosis is based primarily upon clinical signs and muscle biopsy results. Fine-needle aspiration cytology of affected muscles is an alternative to muscle biopsy that may provide evidence of an inflammatory infiltrate. EMG of the extraocular muscles may reveal abnormalities. A creatine kinase level was measured in one dog and found to be normal. In a recent report, marked swelling of the dorsal rectus muscles was evident on ultrasonography of the globe. Histopathologic findings on muscle biopsy



Fig. 13.8. Bilateral exophthalmos in a dog with extraocular myositis (Courtesy of Dr. James Carpenter, reprinted with permission¹⁷⁶).

include inflammatory infiltrates with myofiber necrosis and phagocytosis, as well as areas of hemorrhage. In one dog that was euthanized and necropsied (no therapy attempted), all extraocular muscles except the retractor bulbi musculature were abnormal. No other muscle groups were affected.

- d. Clinical signs resolved spontaneously in one dog and in all the remaining dogs that were treated with oral immunosuppressive glucocorticoid therapy. One dog relapsed following glucocorticoid discontinuation, but responded favorably to reinstitution of therapy. The prognosis for this disorder appears to be favorable.
3. Laryngeal/pharyngeal myositis¹⁷⁸
 - a. Laryngeal and pharyngeal dysfunction associated with evidence of localized inflammatory myopathy has been described in three dogs, including a 7-yr-old male Boykin spaniel, a 10-yr-old male Malamute, and a 3-yr-old female Bouvier des Flandres. The pathogenesis is unknown.
 - b. Clinical signs were consistent with laryngeal paralysis (see Chapter 12) and dysphagia of chronic duration.
 - c. Diagnosis was based upon EMG abnormalities largely restricted to the laryngeal and pharyngeal musculature, and histopathologic evidence of an inflammatory myopathy (e.g., inflammatory infiltrates, myofiber necrosis and phagocytosis) restricted to the laryngeal and pharyngeal musculature. In one dog, there was evidence of mild focal inflammation in the temporalis musculature.
 - d. Treatment protocols and prognosis for this disorder are as of yet undetermined, due to the small number of cases. One dog was euthanized due to respiratory distress, one was treated surgically (laryngoplasty), and one responded to a combination of corticosteroids and thyroid replacement therapy.
4. Autoimmune polymyositis^{1-3,12,114,179-185}
 - a. This is an autoimmune inflammatory disease of unknown pathogenesis primarily affecting the appendicular muscles. It is more commonly reported in dogs than cats. While there is usually no identifiable cause for the immune response, systemic lupus erythematosus, the use of trimethoprim-sulfa drugs in Doberman Pinschers, and thymomas (usually in conjunction with acquired myasthenia gravis) have all been associated with the development of this condition.
 - b. While any age or breed of dog can be affected, most are middle-aged large-breed dogs of either sex. A group of seven Newfoundland dogs with autoimmune polymyositis, ranging in age from 6 mo to 5 yr of age, was recently described. Clinical signs may be acute or chronic and may include generalized weakness that is often worsened by exercise, hyperesthesia upon muscle palpation (myalgia), regurgitation (due to megaesophagus), dysphagia, depression, fever, muscle swelling acutely, muscle

atrophy chronically, shifting leg lameness, and voice change. None of the reported Newfoundlands exhibited myalgia.

- c. Diagnosis is based upon typical clinical findings, as well as results of various diagnostic tests. Creatine kinase levels may be elevated, EMG examination typically reveals abnormalities, and muscle biopsy reveals myofiber necrosis, phagocytosis, and regeneration, with a nonsuppurative inflammatory infiltrate. Immunoglobulin localization to the sarcolemma may also be demonstrable immunohistochemically.
 - d. Treatment consists of oral prednisone therapy at immunosuppressive doses (e.g., 1–2 mg/kg, q 12 hr) until clinical remission is achieved, with subsequent tapering of the dose. The prognosis is generally favorable, although relapses may occur.
5. Dermatomyositis^{2,3,12,13,114,186–196}
- a. Best described in Collie dogs, this is an inflammatory disorder of skin, and to a lesser extent muscle, that is believed to be immune-mediated (autoimmune) and heritable as an autosomal dominant trait. This disorder is also recognized in Shetland sheepdogs and has been reported in a Pembroke Welsh Corgi, as well as an Australian Cattle dog.
 - b. Clinical signs of dermatitis usually begin between 2 and 6 mo of age in Collies and Shetland sheepdogs. Skin lesions predominate in the facial area, especially the nose, lips, and tips of the ears (Fig. 13.9). Some dogs will develop lesions around bony prominences of the lower limbs and sternum. Clinical signs of myositis are typically mild or inapparent (especially in Shetland sheepdogs) and develop after the skin lesions are noticed.



Fig. 13.9. Characteristic skin lesions in a dog with dermatomyositis (Courtesy of Dr. Chris Rees).

Some dogs may have only temporal and masseter muscle atrophy. Other dogs may develop more prominent signs of a myopathy, such as a stiff gait with exercise intolerance, megaesophagus, and dysphagia. Clinical signs associated with both the dermatitis and myositis tend to wax and wane and most dogs resolve spontaneously by 6–8 mo of age.

- c. Diagnosis is based mainly upon signalment and clinical signs. Creatine kinase levels are usually normal, but EMG evaluation usually reveals abnormalities in patients with myositis. Skin and muscle biopsies confirm the inflammatory disorder. In addition to inflammatory infiltrates in these biopsies, evidence of vasculitis is sometimes evident.
 - d. Although the efficacy of immunosuppressive oral prednisone therapy is questionable, an initial dose of 1–2 mg/kg q 12 hr, with subsequent tapering, is recommended. Since the disease tends to resolve spontaneously without therapy, it is difficult to assess the efficacy of this treatment. Hypoallergenic shampoos are also recommended. The prognosis is typically good for recovery.
6. Feline hyperesthesia syndrome (FHS)^{197–201}
- a. Feline hyperesthesia syndrome is a well-described, yet poorly understood disorder of unknown etiology. Affected cats intermittently display clinical signs suggesting an irritative phenomenon, and proposed causes have included behavioral and seizure disorders. There is recent evidence that FHS represents a myopathy, with histopathologic muscle biopsy features similar to inclusion body myositis of human beings. Inclusion body myositis is a common idiopathic inflammatory myopathy of elderly people. Muscle biopsies from such patients contain numerous rimmed vacuoles (inclusion bodies) containing proteins that are commonly found in brains of Alzheimer's patients (e.g., paired helical filaments, presenilin I, beta-amyloid precursor protein). Similar inclusions were recently identified in epaxial muscle biopsy samples from cats with FHS. Inclusion body myositis is believed to be a degenerative myopathy, with a secondary immune-mediated inflammatory response.
 - b. Any age, breed, or sex of cat can develop FHS. There may be a predisposition for FHS to develop in Abyssinians, Burmese, Himalayans, and Siamese breeds. In a recent report, affected cats were all between 5 and 8 yr of age at the onset of dysfunction. Clinical signs of the disorder include the following: rippling of the skin over the dorsum; muscle spasms in the thoracolumbar epaxial region; violent licking and biting at the back, flank area, pelvic limbs, and/or tail; agitated demeanor, apparently startling easily; excessive vocalization (e.g., growling, hissing, meowing); pupillary dilation; exaggerated tail motion; attacking inanimate objects or people; and running frantically. These abnormalities tend to occur episodically. Affected cats resent palpation of the thoracolumbar epaxial musculature. There are no neurologic deficits in cats with FHS.

- c. Diagnosis is based primarily on historical complaints and clinical signs. Bloodwork, spinal imaging, infectious disease titers, CSF analysis, and EEG evaluations are typically normal. Spontaneous EMG activity was documented in the thoracolumbar epaxial muscles of FHS cats in a recent report. All cats in this study had epaxial muscle biopsy findings similar to those found in human inclusion body myositis. Rimmed intramyofiber vacuoles, containing paired helical filaments and beta-amyloid, were found in biopsies from all affected cats.
 - d. Feline hyperesthesia syndrome tends to progress over one to several years. Similar to human inclusion body myositis, no effective therapies have been identified for FHS. The prognosis for control of this disease syndrome is poor.
7. Infectious myositis^{1,3,12,13,19,82,202-213}
- a. Although infectious myositis is relatively uncommon, there are numerous microbial agents that can lead to myopathies in dogs and cats. A detailed description of all these infectious myopathies is beyond the scope of this text. Most infectious myopathies are polymyopathies and represent a facet of multisystemic illness. Viral associated myopathies are rare, but feline immunodeficiency virus (FIV) has recently been shown to induce a sub-clinical myopathy in experimentally infected cats. Clostridial species are most commonly implicated in bacterial myositis; these infections may be focal, involving one or several muscles in one limb. *Leptospira* species have also been associated with myositis in dogs. Protozoal myopathies include those due to *Toxoplasma gondii*, *Neospora caninum*, *Hepatozoon canis*, and *Babesia canis* and *gibsoni*. *Sarcocystis* species have been identified in canine and feline skeletal muscle, but evidence of clinical disease is lacking. Myositis can also be due to rickettsial infection (e.g., ehrlichiosis, Rocky Mountain spotted fever). Rarely, parasitic infestations (e.g., *Trichinella spiralis*, *Ancylostoma caninum*, and *Trypanosoma cruzi*) are associated with myositis.
 - b. Clinical signs typically include fever and myalgia. With bacterial infections, there may be a recent history of a bite wound or surgery. Clostridial infections are often characterized by palpable crepitus, due to gas accumulation in tissues. *Toxoplasma* and *Neospora* infections in young dogs often result in rigid hyperextension of the pelvic limbs, due to a combined neuropathy/myopathy (see Chapter 12). Typical clinical findings in dogs with hepatozoonosis often include chronic myalgia, fever, cachexia, anorexia, lethargy, paresis, oculonasal discharge, and bloody diarrhea.
 - c. Diagnosis of an infectious myositis is based upon demonstrating the presence of a likely causative infectious organism in a patient with myositis. In some cases, organisms are found in muscle biopsy samples; in others, serial serology or wound culture is necessary to identify the organism's presence. Creatine kinase levels are likely to be elevated, and basic bloodwork may

result is uncontrolled and sustained skeletal muscle contraction, most evident in extensor muscles. The autonomic nervous system can also be affected by tetanospasmin toxin.

- b. Tetanus can be localized (i.e., involving one region of the body, such as the head or one limb) or generalized. Localized tetanus often progresses to generalized tetanus, but some cases may remain localized throughout the disease course. The onset of clinical tetanus after sustaining a wound or surgical contamination (if this is part of the history) is variable. The range is from 3–18 days, most often 5–10 days. Since cats are more resistant to the tetanus toxin, the delay may be up to 3 wk. In dogs, evidence of an active infection is often elusive and may not be present. Cats with tetanus typically will have a readily evident source of infection and toxin production. Muscle stiffness is the hallmark of tetanus in dogs and cats, whether it is localized or generalized. Localized tetanus of a limb is often associated with a wound on the affected limb. The affected limb is typically stiff and hyperextended. The stiffness may spread to the opposite limb (e.g., both pelvic limbs) and continue to progress to the thoracic limbs. Localized tetanus of the head region can also occur. This may represent an early stage of generalized tetanus after hematogenous spread of the toxin, with the shorter cranial nerves affording a more rapid delivery of toxin to the CNS than the motor nerves of the extremities.

Involvement of muscles around the head usually leads to very characteristic features. Facial muscle contraction is evidenced by narrowed palpebral fissures and drawing back of the lips (*risus sardonicus*) as well as wrinkling of the forehead with the tips of the ears being pulled toward each other (Fig. 13.10). Extraocular muscle involvement leads to *enophthalmos* with protrusion of the third eyelids, and masticatory muscle contraction results in an inability to open the mouth (*trismus*, or “lockjaw”). Laryngeal and pharyngeal musculature may also be affected, with resultant dyspnea (due to laryngospasm) and dysphagia, respectively. Increased respiratory rate is common in tetanus, due to involvement of both laryngeal and lower respiratory musculature. Affected animals often seem willing to eat, but have difficulty prehending and swallowing food.

Generalized tetanus is more common than localized, and many localized cases progress to become generalized. Generalized tetanus is usually characterized by stiffness and extensor rigidity of all limbs, along with the above-described clinical abnormalities involving the head region. If the patient remains ambulatory, the gait will be stiff and stilted, and a wide-based, “saw-horse” stance will be evident. If the patient is recumbent, the limbs are often held out in rigid hyperextension, with the tail curved dorsally (Fig. 13.11). Reflex muscular spasms tend to occur in response to tactile or auditory stimuli. Because of increased urethral and anal sphincter tone, urine retention and constipation often occur in tetanus patients.



Fig. 13.10. Typical facial features of tetanus in a dog.



Fig. 13.11. Cat with generalized tetanus, exhibiting rigid extension of all limbs and dorsiflexion of the tail.



Fig. 13.12. Bilateral pelvic limb dysfunction in a cat with ischemic neuromyopathy (Courtesy of Dr. Gregg Kortz).

2. Cats of any age, breed, or sex can be affected, but males tend to predominate. Persians and domestic shorthaired cats may also be overrepresented. Typically, there is an acute or peracute onset of pelvic limb dysfunction (Fig. 13.12) and signs of pain. While the severity of dysfunction may vary, most cats are either nonambulatory paraparetic or paraplegic. The signs may or may not be symmetric. The gastrocnemius and cranial tibial muscles are usually firm and painful to palpation, the nail beds of the pelvic limbs are cyanotic, and the distal aspects of the pelvic limbs are cool to the touch, compared to the thoracic limbs. There is usually an inability to flex or extend the tarsal joint, although the ability to flex and extend the hip and stifle joints is usually preserved. Femoral pulses are characteristically difficult or impossible to palpate. In most cases, there is also analgesia of the digits and tarsal area.

Clinical signs in dogs are more variable than cats. In general, dogs tend to have more protracted clinical signs, varying from subacute to chronic. Some patients may even display intermittent clinical signs referable to the pelvic limbs. In general, pelvic limb lameness, paresis, and paralysis occur in dogs with aortic thromboembolism. Abnormal pelvic limb reflexes, cool extremities, evidence of pain, and decreased digital sensation are also observed in dogs with this disorder.

3. A tentative diagnosis is based primarily upon signalment, history, and characteristic clinical findings. Cats, and some dogs, will have evidence of cardiomyopathy on thoracic radiographs and/or echocardiography. Serum creatine

kinase levels are markedly elevated. Some patients are also acidotic and hyperkalemic. Evidence of disseminated intravascular coagulation (DIC) may also be elucidated (low platelet count, prolonged activated clotting time, etc.). While not commonly performed, electrodiagnostic tests will support the diagnosis of a neuromyopathy. Histopathology of nerve and muscle, if performed, will reveal axonal loss and myofiber necrosis, respectively. A variety of disease conditions have been associated with canine aortic thromboembolism and include cardiac disease, neoplasia (neoplastic emboli), renal dysfunction, and endocrine disorders (e.g., hypothyroidism). In both dogs and cats, ultrasonography and arteriography may be helpful in confirming the presence of thromboembolic disease.

4. No treatment has been proven to be effective in improving the outcome of these patients. Suggested therapies directed specifically at the thromboembolic problem have included aspirin therapy, administration of plasminogen activators, administration of anticoagulants (e.g., heparin, coumarin), administration of vasodilatory agents (e.g., acepromazine), and catheter or surgical (not currently recommended, especially in dilated cardiomyopathy) embolectomy. Attendant conditions, such as acidosis, hyperkalemia, and DIC, should be addressed. Specific treatment for cardiomyopathy is also recommended in cats, and in those dogs with cardiac disease. In dogs, the treatment and prognosis are variable, largely dependent upon the underlying disease. In cats, although many will recover pelvic limb function within 6 wk to 6 mo, the prognosis is poor. Most cats will re-embolize and/or succumb to heart disease within a 6 mo period. Prophylactic aspirin therapy (25 mg/kg, every third day) has been recommended for recovering and recovered cats, but there is no evidence of efficacy.

E. Traumatic

1. Infrapinatus contracture^{3,228-231}

- a. This is an uncommon injury encountered mainly in hunting and working dogs. Damage with subsequent contracture of the infrapinatus muscle results in a characteristic thoracic limb gait abnormality. Muscle fibers of the damaged infrapinatus are replaced by fibrous connective tissue. Further development of periarticular connective tissue contributes to clinical signs of lameness. A similar disorder has been reported associated with injury to the teres minor muscle.
- b. Hunting and working dog breeds are most commonly affected by this myopathy; there is no age or sex predilection. Bilateral involvement has been reported, but is very uncommon. The typical gait abnormality often develops 2-6 wk after an acute shoulder injury. There is usually a history of an acute thoracic limb lameness that improves or resolves with rest and anti-inflammatory drugs, following which a chronic gait abnormality develops. The typical gait of infrapinatus contracture is characterized by elbow adduction, with excessive lateral or outward rotation (abduction) of



Fig. 13.13. Typical thoracic limb carriage in a dog with infraspinatus contracture (Courtesy of Dr. Alexander de Lahunta).

the humerus. Affected dogs may hold the thoracic limb in this position while stationary (Fig. 13.13). When walking, these dogs often exhibit a compensatory “flip” of the carpus on the affected limb. Limited range of motion of the shoulder joint may also be appreciated. Atrophy of scapular musculature associated with the affected limb is often evident.

- c. Diagnosis is based primarily upon historical and clinical features. Ultrasonography of the shoulder region may allow identification of the abnormal infraspinatus muscle. Electromyographic abnormalities are often present, but the damaged muscle may be electrically silent (e.g., if virtually replaced by fibrous connective tissue). Muscle biopsy confirms fibrous connective tissue replacement of muscle fibers.
- d. Treatment consists of surgical tenomyectomy of the abnormal infraspinatus, with removal of all visible periarticular fibrous tissue. Prognosis for recovery is excellent following surgery.

2. Iliopsoas muscle injury²³²
 - a. Pelvic limb lameness due to a suspected strain injury to the iliopsoas musculature has been reported in three adult dogs.
 - b. One dog experienced an acute onset of pelvic limb lameness, the other two dogs exhibited chronic lameness. One of the affected dogs exhibited bilateral pelvic limb involvement. All dogs displayed signs of discomfort upon extension of the associated coxofemoral joints. The dogs with bilateral involvement stood with external rotation of the pelvic limbs ("cow-hocked").
 - c. Diagnosis was based upon finding pain associated with the iliopsoas muscle on clinical examination, as well as demonstrating abnormal iliopsoas musculature on ultrasonography (e.g., hypoechoic, swollen musculature). A painful (hyperesthetic) response was appreciated upon palpation of the affected iliopsoas muscle(s), at the lesser trochanter, ventromedial to the ilium, and/or per rectum. Also, simultaneous internal rotation and extension of the affected coxofemoral joint elicited pain in all three dogs.
 - d. All dogs responded well to rest and treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Lameness recurred in one dog despite rest and NSAID therapy. This dog responded well to tenomyectomy of the iliopsoas muscle.
3. Quadriceps contracture (stiff stifle syndrome)^{3,73,233}
 - a. This is a phenomenon most commonly associated with inadequate fracture repair and/or prolonged immobilization of distal femoral fractures in young dogs, especially of large breeds. Other conditions, such as osteomyelitis of the femur, may also lead to this sequela. Inflammation and fibrous tissue proliferation cause adhesions between the quadriceps muscle group and the femur. With prolonged disuse of the limb, periarticular fibrosis of the stifle develops.
 - b. Clinical signs typically include progressive pelvic limb extension and lameness following an orthopedic injury. Muscle contracture and disuse atrophy often progress to the point that the limb is nonfunctional. The affected limb is usually abducted, and there is severe limitation of the range of motion in the stifle joint.
 - c. Diagnosis is based on characteristic historical and clinical features. Muscle fiber size variability, fibrosis, and necrosis are characteristic muscle biopsy features. Extensive muscle fiber atrophy, predominantly affecting Type I fibers, is also typical.
 - d. Proposed treatments for quadriceps contracture include surgical breakdown of fibrous tissue, Z-plasty of the quadriceps muscle group, and stifle arthrodesis in a functional walking angle. In general, the prognosis for a functional limb once contracture has developed is guarded to poor. Efforts should be focused on preventing this condition.
4. Gastrocnemius muscle avulsion^{234,235}
 - a. Avulsion or rupture of the proximal attachment of the gastrocnemius muscle has been reported sporadically in dogs. There is usually a known

disease course. In dogs exhibiting discomfort associated with the tail, administration of analgesic drugs is recommended. Minimizing prolonged cage transport and ensuring a regular training schedule are suggested preventive measures.

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Chapter 14

JUNCTIONOPATHIES: DISORDERS OF THE NEUROMUSCULAR JUNCTION

Jacques Penderis

I. Introduction

By the very name, the term “neuromuscular junction” (NMJ) describes the junction between an efferent nerve (in the context of the diseases discussed in this chapter usually a somatic efferent nerve) and the muscle innervated by that nerve. Pathological processes that affect the NMJ are commonly referred to as junctionopathies.

II. Normal Anatomy and Physiology of the Neuromuscular Junction¹⁻⁹

The NMJ can be subdivided into three basic components: the presynaptic membrane, the synaptic cleft, and the postsynaptic membrane in the end-plate region of a skeletal muscle fiber. The NMJ is part of the acetylcholine (ACh) group of neurotransmitter systems. ACh neurotransmitter systems are also found in autonomic ganglia and parasympathetic effector junctions in the peripheral nervous system, in the spinal cord, and in the brain (particularly as a major component of the ascending reticular activating system). Each motor neuron innervates a number of muscle fibers (myofibers); combined, these are termed a motor unit. For successful NMJ transmission to occur, the action potential traveling down a motor neuron to a myofiber must be successfully propagated to the end-plate region of the innervated muscle fiber. The arriving action potential at the level of the nerve terminal results in depolarization of this region and consequent opening of calcium (Ca^{2+}) channels on the axolemma surface. The increased cytosolic concentration of Ca^{2+} triggers exocytosis of ACh by causing ACh-containing vesicles to dock and fuse with the plasmalemma at the synaptic cleft region. Three classes of proteins are involved in the process of ACh exocytosis and all three are vulnerable to toxins and disease processes:

- Synapsin I (controls the availability of synaptic vesicles) and synaptotagmin (associates with N-type Ca^{2+} channels)
- Synaptobrevin (vesicle-associated membrane protein), syntaxin and synaptosome-associated protein 25, which are all essential components of the exocytosis process
- N-ethyl-maleimide-sensitive fusion protein (NSF) and soluble NSF-attachment proteins, which are all involved in neurotransmitter release

The released ACh molecules cross the synaptic cleft to reach the ACh receptors, located on the end-plate region of the skeletal muscle fiber. The ACh receptor molecules are integral membrane proteins consisting of five subunits and function as

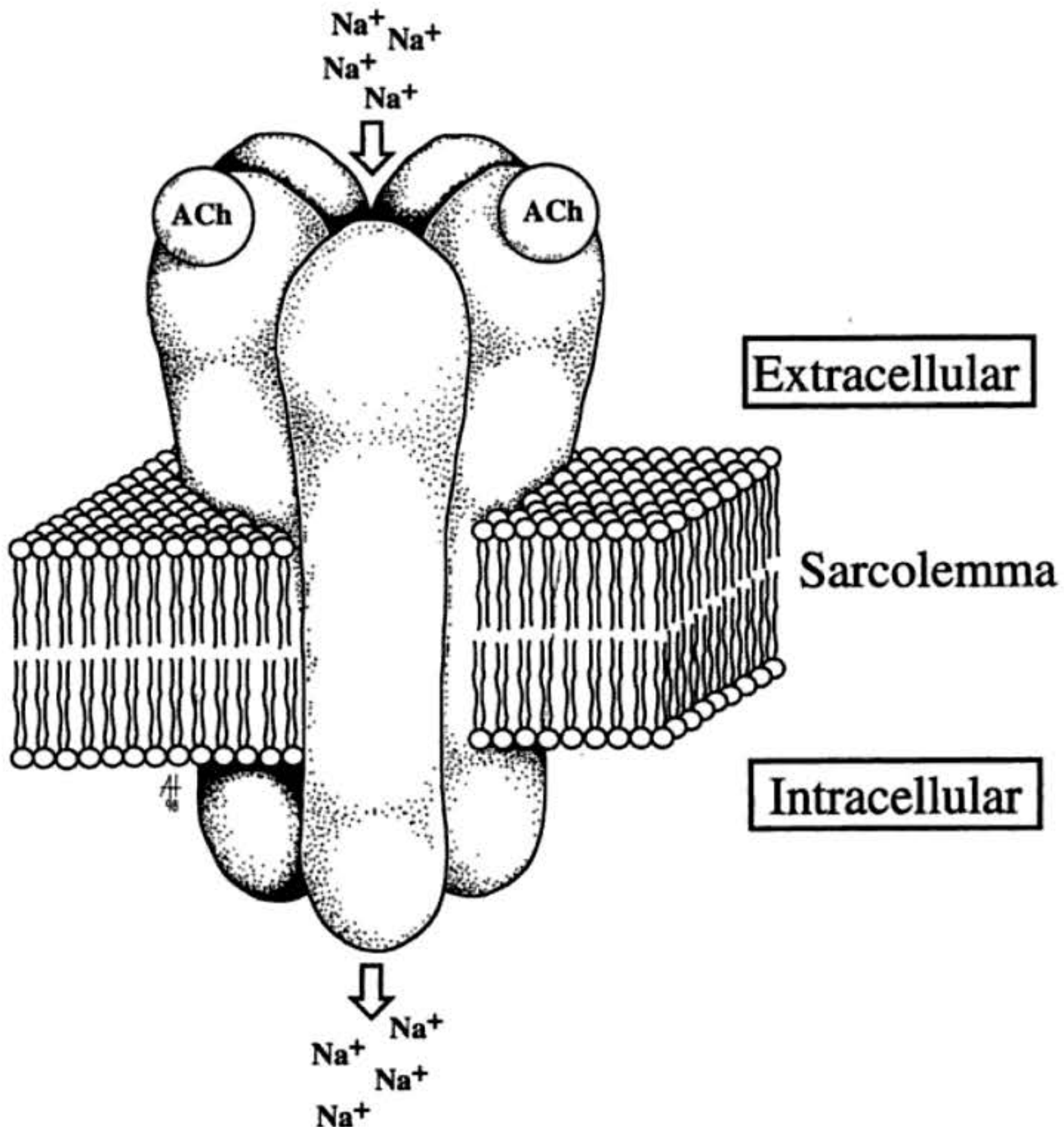


Fig. 14.1. The ACh receptor consists of five subunits arranged in a circular shape around the central Na^+ channel. The ACh binding sites are located on the extracellular portion of the two α -subunits. Binding of ACh to the ACh binding sites results in opening of the Na^+ channel and Na^+ influx into the muscle cell (Illustration by Anton Hoffman, reprinted with permission³⁴).

sodium (Na^+) channels. The five subunits are arranged in a circular shape around the central Na^+ channel (Fig. 14.1). Located on the extracellular portion of the alpha (α)-subunit (of which there are two per receptor molecule) are the ACh binding sites. Binding of ACh to the ACh binding sites results in opening of the Na^+ channel and Na^+ influx into the muscle cell. This influx of Na^+ results in depolarization of the end-plate region, termed the end-plate potential (EPP). The EPP has to reach a threshold to result in sufficient spread of the depolarization along the muscle fiber to cause release of the intracellular Ca^{2+} stores and result in muscle contraction.

The magnitude of the EPP depends on the number of ACh receptors activated. In the normal situation, there is an overabundance of both available ACh and ACh receptors and the EPP produced by nerve depolarization therefore usually far exceeds the requirement for muscle contraction; this excess is termed the safety factor of neuromuscular transmission. During repetitive depolarization of the nerve terminal following repeated firing of a motor nerve, there is a decrease in the amount of ACh released into the synaptic cleft with each depolarizing event, a phenomenon termed rundown. In normal individuals, however, the degree of rundown is insignificant due to the large safety factor of neuromuscular transmission. Following successful NMJ transmission, several processes prevent excessive stimulation of muscle fibers. First, the Na^+ channels that open following activation of ACh receptors do so only transiently before closing and becoming refractory for a few seconds. Second, shortly after its release into the synaptic cleft, the ACh is rapidly eliminated by both diffusion away from the cleft region and by hydrolysis by ACh esterase in the cleft region.

III. Vulnerability of the Neuromuscular Junction

Disorders affecting neuromuscular transmission are usually classified as pre- or post-synaptic, although some disease processes may affect both. Processes affecting neuromuscular transmission may either increase or decrease the activity of this system and do so by:

- Increasing or decreasing presynaptic ACh release, as a result of altering ACh synthesis, transport, reuptake or presynaptic release
- Altering the concentration or duration of ACh effect in the synaptic cleft, as a result of altered removal of ACh from the synaptic cleft
- Acting as an ACh agonist or antagonist at the NMJ by affecting the interaction between ACh and the postsynaptic receptor

Botulism toxin and α -latrotoxin (a toxin elaborated by the black widow spider) can be used as examples of diseases affecting the same component of neuromuscular transmission in opposite manners but with the same end result of failure of neuromuscular transmission. Botulism light-chain toxin (the entry of which through the plasmalemma is facilitated by the heavy-chain toxin) blocks synaptic transmission by cleaving synaptic vesicle fusion proteins required for the process of exocytosis. In contrast, α -latrotoxin causes massive ACh release at the NMJ by apparently increasing the probability of vesicle fusion with the plasmalemma and inhibiting vesicle recycling.

A. Vulnerability of the axonal transport system

Although not specifically disorders of the NMJ, substances may interfere with normal neuronal and axonal functions, resulting in disruption of normal anterograde transport of material essential for neurotransmitter synthesis (including

ACh at the NMJ). An example would be vincristine, which nonspecifically blocks axonal transport.

B. Vulnerability of the presynaptic functions

The functions within the presynaptic region are involved in the reuptake of choline from the synaptic cleft, the synthesis of ACh, and the storage thereof in synaptic vesicles, with a large number of substances and disease processes known to target these processes.

Examples of substances affecting these pathways include:

- The Na⁺-dependent high-affinity choline transport system is specifically targeted by hemicholinium, which competes with choline for uptake by the choline-carrier and inhibiting choline uptake, thereby resulting in NMJ blockade.
- The enzyme choline acetyltransferase, involved in ACh synthesis, is targeted by a number of substances including the naphthoquinones and halogenated cholines, which have been shown to be effective enzyme inhibitors in vitro. Choline acetyltransferase is also targeted by false cholinergic neurotransmitters, including triethylcholine and diethylaminoethanol, which are acetylated by the enzyme, stored in synaptic vesicles, but on synaptic release display cholinergic agonist activity below that of ACh (cholinergic hypofunction).
- Vesamicol (an experimental substance) is one of a number of substances shown to induce neuromuscular blockade by blocking the transport of ACh into synaptic vesicles.

C. Vulnerability of presynaptic release of ACh

Numerous toxins target the presynaptic release of ACh. Botulinum toxin and certain snake toxins (including mojave toxin and β -bungarotoxin, among others) block the release of ACh from motor axon terminals. As previously discussed, α -latrotoxin (from the black widow spider) causes NMJ blockade by targeting the same part of the system, but instead by causing massive ACh release.

D. Vulnerability of ACh esterase

Numerous naturally occurring and synthetic substances target the ACh esterase system, resulting in increased synaptic residence of ACh and therefore excessive stimulation following ACh release. Some of the substances bind to the ACh esterase active site for varying times (including edrophonium, physostigmine, and neostigmine) while others interact with the active center to form stable complexes (e.g., organophosphorous compounds).

E. Vulnerability of nicotinic muscle receptors

A wide variety of compounds target the nicotinic receptors, either throughout the nervous system or specific to only the nicotinic receptors of muscle. For example the snake toxin α -bungarotoxin (from the krait *Bungarus multicinctus*) blocks the nicotinic muscle receptors, but those in peripheral autonomic ganglia appear

resistant. The compounds affecting the nicotinic muscle receptors include, among others, strychnine (the indole alkaloid from the *Strychnos* spp.), many snake toxins, anatoxin- α from blue-green algae and curare-like substances.

IV. Clinical Presentation of Neuromuscular Transmission Syndromes^{1,7,9,10}

Neuromuscular junction transmission disorders are frequently classified as either presynaptic or postsynaptic. Irrespective of the cause of failure of neuromuscular transmission, the presenting clinical signs may often be very similar in character. Junctionopathies usually present as symmetric, progressive muscle weakness of both the thoracic and pelvic limbs (Fig. 14.2). Tendon reflexes are often intact in the early stages of the disease, which is a useful method to distinguish these diseases from peripheral neuropathies. The NMJ transmission syndrome frequently demonstrates a predilection for certain muscle groups, particularly the small, rapid-movement muscle groups. For this reason, failure of certain cranial nerve musculature may be apparent, including failure of the extraocular muscles and muscles controlling the palpebral reflex and alterations in the voice (dysphonia) and swallowing. Sensory function and level of consciousness are typically unaffected. In some postsynaptic disorders (e.g., organophosphorous compound poisoning), there may be additional cholinergic signs, including lacrimation, miosis, and bradycardia.

In most cases, removal of the source of NMJ blockade will result in rapid resolution of the clinical signs, but in some cases there is tight binding of the agent to the NMJ (e.g., botulism) and recovery may take a prolonged period of time.

Based on the classification of NMJ transmission disorders, examples of mainly presynaptic agents include: botulinum toxin, tick saliva, and black widow spider venom. Examples of postsynaptic agents include: anticholinesterase agents, tetracycline antibiotics, and interferon- α . Most of the toxic NMJ transmission disorders include a combination of both presynaptic and postsynaptic blockades and include: snake evenomation, aminoglycoside antibiotics, and polymyxin antibiotics.

V. Myasthenia gravis (MG)

A. Congenital myasthenia gravis¹⁰⁻¹⁶

1. Congenital MG is due to an abnormal reduction in the number of ACh receptors on the muscular end plate, resulting in clinical signs of exercise-induced weakness.
2. The disorder has been described in a number of breeds, including Springer spaniels, Jack Russell terriers, smooth-haired Fox terriers, and Samoyeds. Although reported, congenital MG is rare in the cat. Clinical signs of recurrent and progressive muscle fatigue usually become apparent between 6 and 9 wk of age. Multiple pups in a litter are usually affected. In both the terrier breeds, autosomal recessive inheritance has been demonstrated. A myasthenic syndrome, inherited as an autosomal recessive disorder, has been described in the Gammel Dansk Hovsehund dog where a presynaptic disorder interferes

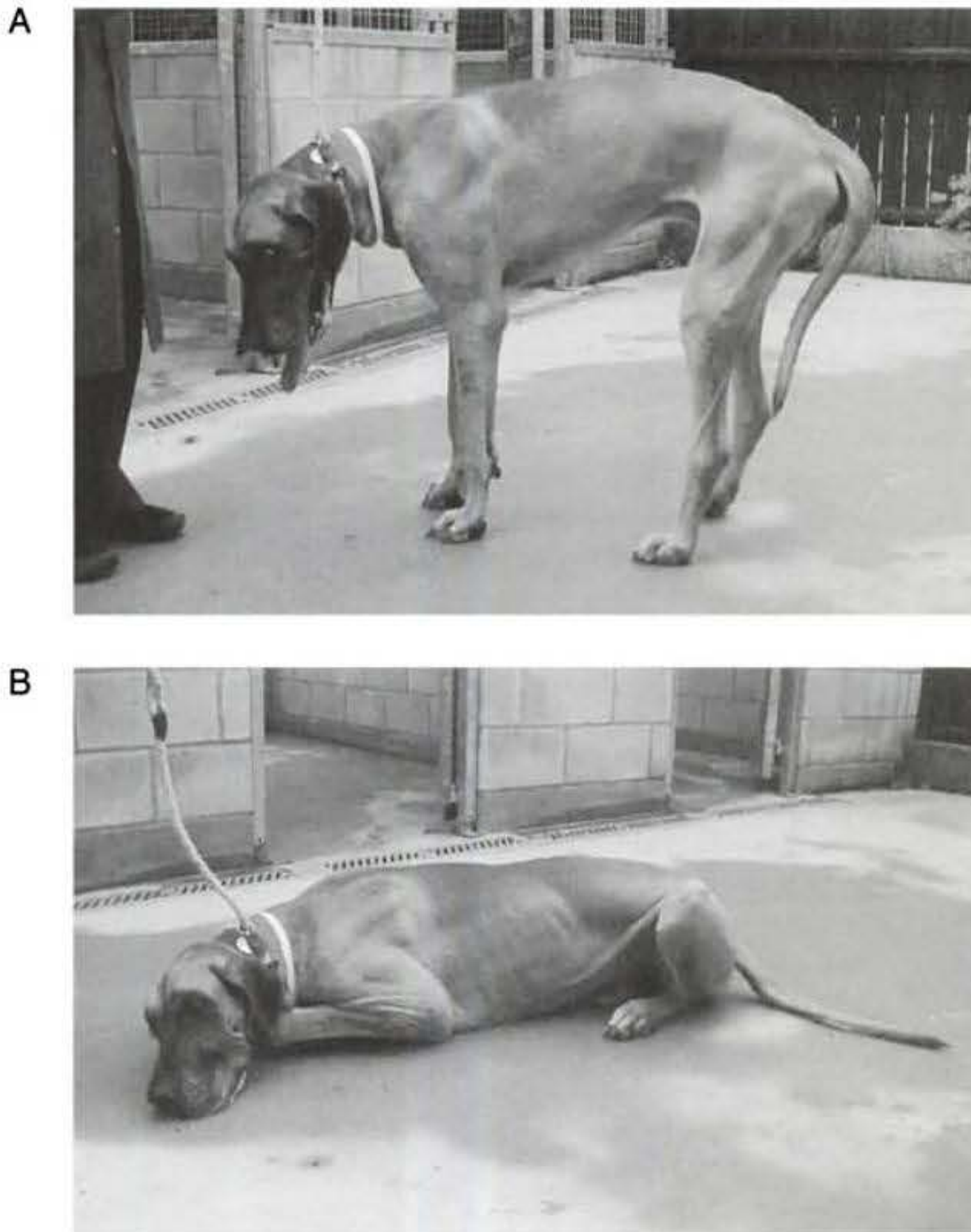


Fig. 14.2. Great Dane with acquired exercise intolerance demonstrating (A) exercise-induced weakness with cervical ventroflexion and respiratory distress, followed by (B) collapse into ventral recumbency.

with ACh release. In breeds other than the Gammel Dansk Honsehund, congenital MG is characteristically a progressive disorder, and affected dogs are often unable to walk. All breeds may be predisposed to developing aspiration pneumonia, although megaesophagus is typically demonstrable only in the smooth-haired Fox terrier.

3. Due to the absence of antibodies to ACh receptors in congenital MG, diagnosis is by signalment, history, and a suitable response to anticholinesterase drugs. Ultrastructural demonstration of decreased ACh receptors on muscle biopsy may be possible to confirm the postsynaptic disorder (Fig. 14.3).

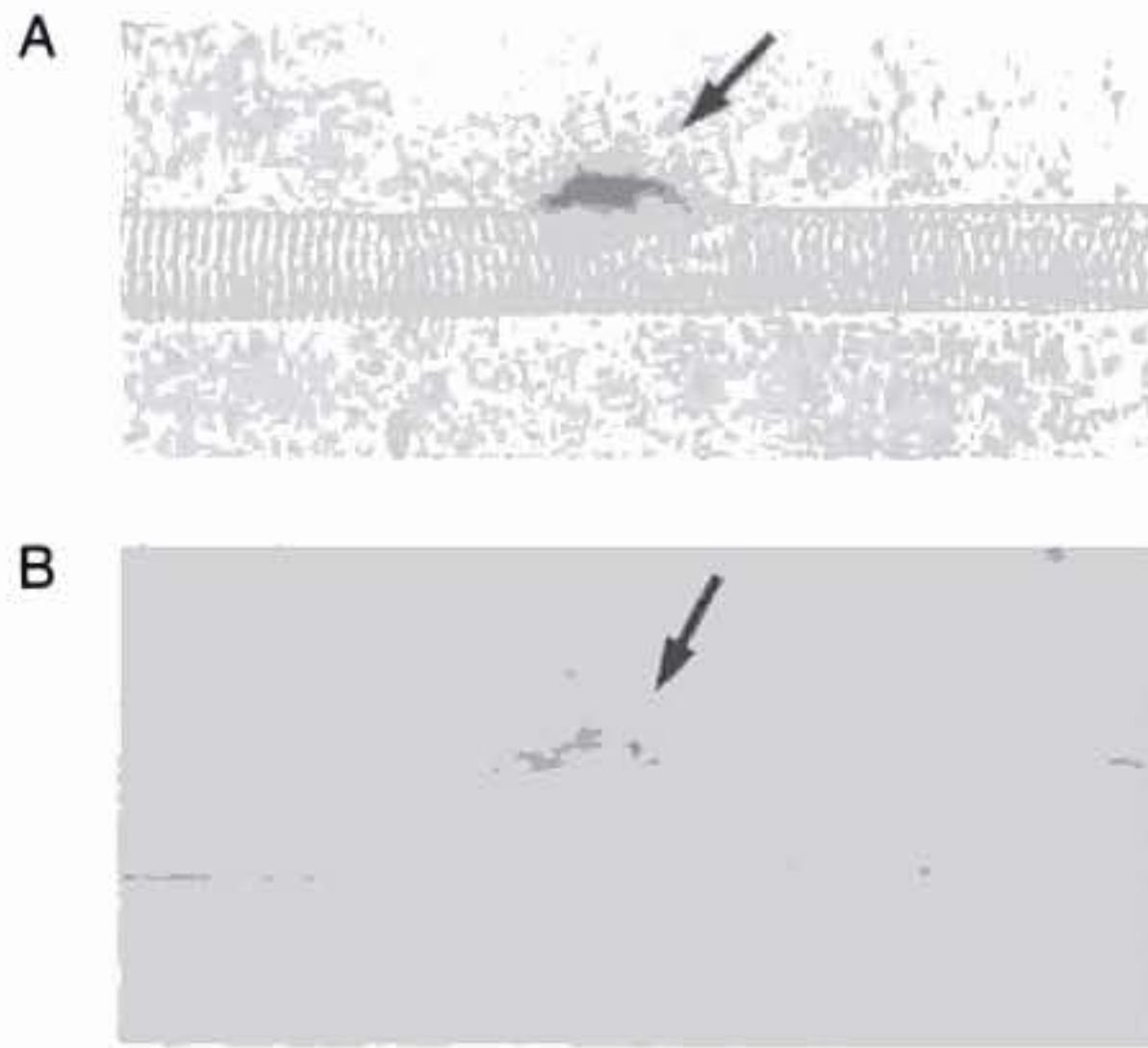


Fig. 14.3. Normal ACh receptor concentration in a control 4-mo-old Jack Russell terrier (arrow) (A) and dramatically decreased ACh receptor numbers in a Jack Russell puppy affected by congenital MG (arrow) (B).

4. Although the extent of clinical responsiveness is often incomplete and unpredictable, anticholinesterase therapy (e.g., pyridostigmine) is recommended for dogs with congenital MG. Remission of clinical disease is unlikely in these cases and lifelong management is therefore required. The prognosis for most cases of congenital MG is guarded to poor. The disorder is often progressive, and affected dogs may develop recurrent or severe aspiration pneumonia.

B. Acquired myasthenia gravis^{2-10,13,16-73}

1. Acquired MG is an autoimmune disease in which antibodies (in most cases IgG) are formed against the nicotinic ACh receptors, resulting in decreased numbers of receptors on the postsynaptic sarcolemmal surface (Fig. 14.4). In the majority of both human and canine cases, these antibodies have been shown to recognize the same epitopes on the ACh receptor. These epitopes are primarily located in the main immunogenic region of the two alpha subunits, on the extracellular surface. The main immunogenic region is in close proximity (although distinct from) the ACh binding site. These autoantibodies alter the receptor function by one of three mechanisms:
 - Antibodies may bind directly to the ACh receptor resulting in a blockade of ion channel opening.
 - Antibodies may increase the degradation rate of ACh receptors by cross-linkage, resulting in a decreased concentration of receptors at the postsynaptic membrane.
 - Complement-mediated lysis of the muscle end plate may take place.

Table 14.1: Clinical Findings in Cats and Dogs with Acquired MG

Clinical Findings	Cats (%)	Cats (n = 20)	Dogs (%)	Dogs (n = 25)
Generalized weakness	70	14	64	16
Decreased palpebral reflex	60	12	36	9
Decreased menace response	50	10		
Decreased gag reflex			32	8
Laryngeal weakness			24	6
Megaesophagus	40	8	84	21
Aspiration pneumonia	20	4	84	21
Cranial mediastinal mass	15	3	8	2
Muscle fasciculations	15	3		
Decreased flexor reflexes	10	2		
Polymyositis	5	1	8	2
Cardiomegaly	5	1		
Muscle atrophy	5	1		

Source: Adapted from Dewey CW, Bailey CS, Shelton GD, et al., Clinical forms of acquired myasthenia gravis in dogs: 25 cases (1988–1995), *J Vet Intern Med* 11: 50–57, 1997; and Ducoté JM, Dewey CW, Coates JR, Clinical forms of acquired myasthenia gravis in cats, *Compend Contin Educ Pract Vet* 21: 440–448, 1999, with permission.

esophagus as compared to the predominantly striated muscle of the canine esophagus.

The generalized form of MG is characterized by appendicular muscle weakness that may be induced or exacerbated by exercise. Typically, severe exercise intolerance develops after only a few minutes of exercise, but following rest the animal regains muscle strength and can return to activity for a short period before a relapse of the muscular weakness. Regurgitation, especially in dogs, may occur secondary to either megaesophagus or a thymic mass. Muscle tremors and decrementing or absent palpebral reflexes may be present as a feature of the muscle weakness. Pharyngeal and laryngeal muscle weakness is evidenced by the presence of excessive drooling, a moist and productive cough (secondary to aspiration pneumonia), and dysphonia. Appendicular muscle weakness tends to be more severe in the pelvic limbs in dogs, whereas this has not been reported in cats. Cats may frequently demonstrate cervical ventroflexion as a clinical sign of generalized weakness; in some cases, such cats may prefer to remain in thoracic recumbency with their heads supported on their thoracic limbs (Fig. 14.5). Generalized MG has been associated with polymyositis in one cat. Third-degree atrioventricular block has been reported to occur concurrently with MG in the dog. Cardiac involvement in MG is well documented in human medicine and may be the result of autoantibodies directed against the conducting tissue of the heart, or a result of secondary focal myocarditis.



Fig. 14.5. Cats with weakness secondary to acquired myasthenia gravis may demonstrate a preference to remain in thoracic recumbency with their heads supported on their thoracic limbs (Photograph courtesy of Dr. Andrew Sparkes, Animal Health Trust, UK).

Acute fulminating MG is a severe and rapidly progressing form of generalized MG. Affected animals demonstrate rapid progression of appendicular muscle weakness and may present nonambulatory in lateral recumbency. Weakness of the skeletal muscles eventually affects the intercostal muscles and/or diaphragm, at which stage affected animals demonstrate severe respiratory distress. Due to the concurrent pharyngeal and laryngeal muscle weakness, aspiration pneumonia is a frequent complication in recumbent patients and the prognosis is therefore poor. Furthermore, for successful treatment, these cases require rapid recognition and intensive care, including respiratory supportive care and possibly plasmapheresis. The prevalence of acute fulminating MG in dogs and cats has been reported as 16% and 15%, respectively.

3. Disorders that may mimic MG include other disorders of the NMJ as well as diseases presenting with generalized or focal weakness of striated muscle. The most important differential diagnoses to consider include:
 - Other disorders of the NMJ, in particular botulism, snake envenomation, tick paralysis, and cholinesterase toxicity
 - Neuropathies and myopathies (particularly inflammatory and breed-related myopathies)

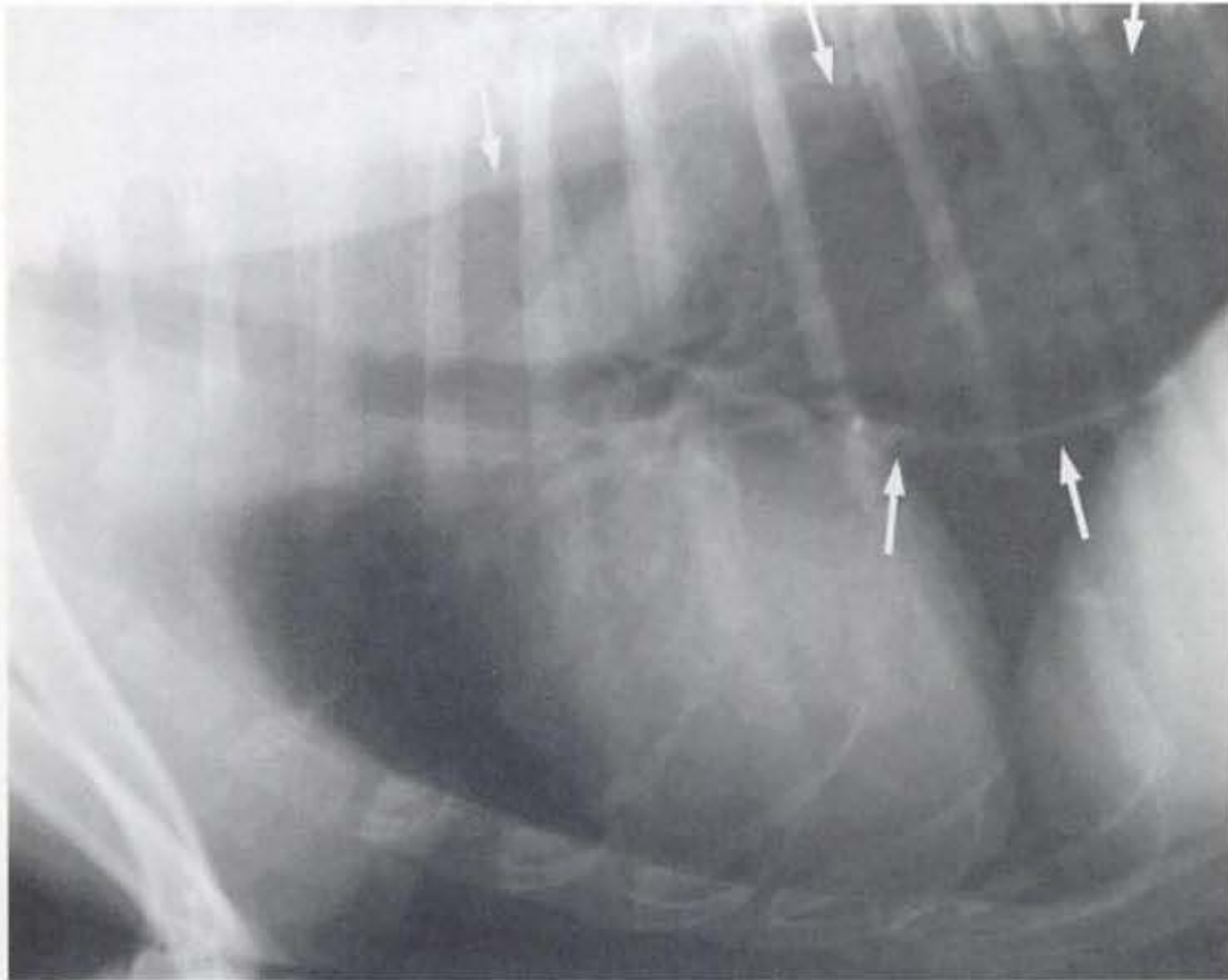


Fig. 14.6. Lateral thoracic radiograph demonstrating megaesophagus in a dog (arrows) with evidence of secondary aspiration pneumonia.

incidence of a cranial mediastinal mass has been reported to be between 15% and 25.7%. The absence of a radiographically demonstrable cranial mediastinal mass does not rule out the possibility of a thymoma. Further imaging, including computed tomography and magnetic resonance imaging, is often helpful in human medicine to evaluate the anterior mediastinum.

An ECG should be performed (particularly if bradycardia is present) to rule out third-degree heart block.

Edrophonium chloride challenge (tensilon response) test

To support the presumptive diagnosis of MG, an edrophonium chloride (Tensilon or Camsilon, Roche Laboratories) challenge test can be performed in animals demonstrating muscular weakness. Edrophonium chloride is an ultrashort-acting anticholinesterase agent, prolonging the residence time of ACh in the synaptic cleft and thereby improving muscle strength where NMJ blockade is present. A positive response to an intravenous injection of edrophonium chloride is supportive of a presumptive diagnosis of MG. An intravenous catheter is placed prior to the challenge test. In dogs, 0.1 to 0.2 mg/kg

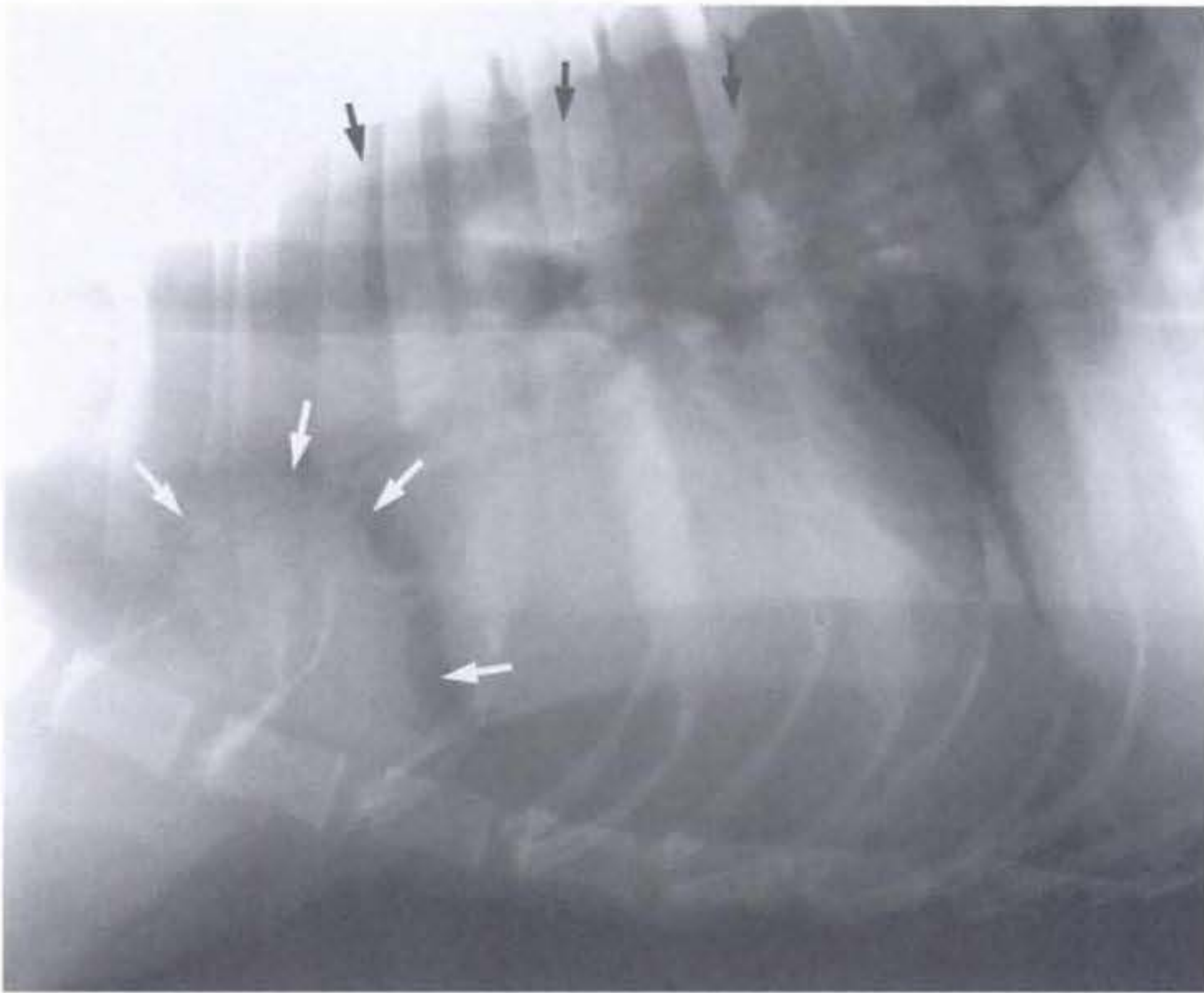


Fig. 14.7. Lateral thoracic radiograph of a dog with MG demonstrating a large cranial mediastinal mass (histopathologically confirmed as a thymoma) (white arrows) and megaesophagus (black arrows).

is administered IV immediately after exercise-induced weakness. In cats demonstrating muscular weakness, a dose of 0.25 to 0.50 mg *per cat* is administered intravenously, after which the patient is observed for evidence of increased muscular activity. A positive response is one in which there is a dramatic increase in muscle strength; this improvement is usually maintained for only a few minutes.

Although edrophonium chloride is relatively safe as a diagnostic agent (due to its short duration of action), atropine should still be available in case a cholinergic crisis is induced. The disadvantages of using edrophonium chloride are primarily the possibility of both false positive and negative results and this test is therefore only used as a guide to revealing the presence of MG. Other disorders causing NMJ block may also demonstrate a partial response to edrophonium chloride, while in those MG patients with insufficient available ACh receptors, an inapparent or small response may be evident, despite

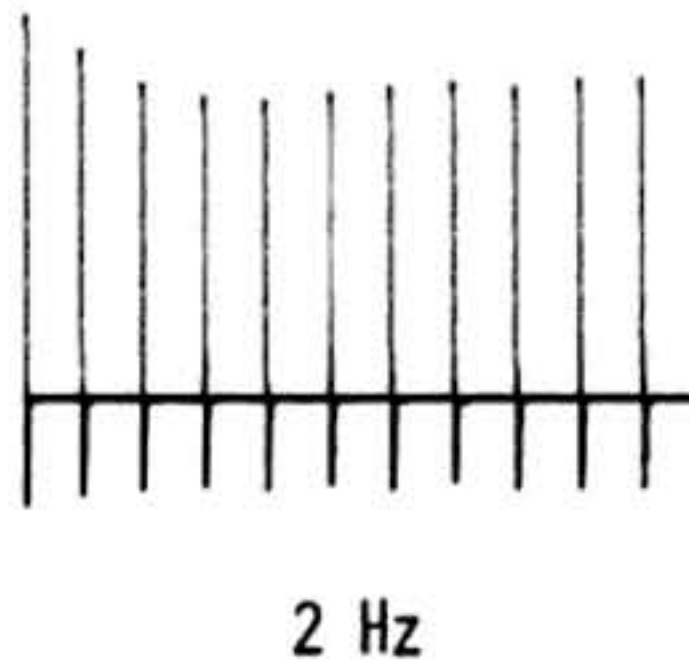


Fig. 14.8. Repetitive nerve stimulation in a Jack Russell terrier with congenital myasthenia gravis, demonstrating progressive decrement of the compound muscle action potential. Normal animals would not demonstrate decrement at stimulation rates less than 5 Hz.

MG than focal MG. Repetitive nerve stimulation in focal MG is still more sensitive than determining serum ACh receptor antibody concentrations in human cases with focal MG. Some other NMJ disorders (e.g., organophosphate toxicity) may also demonstrate a decremental response.

Single-fiber electromyography:

A more specific test for NMJ blockade induced by MG, in both dogs and man, is single-fiber electromyography (SF-EMG). The use of single-fiber EMG is limited at present due to the availability and cost of the recording needles, as well as expertise required to perform the test. Single-fiber EMG is based on obtaining recordings of the evoked action potential from single muscle fibers using a special recording needle with a very small recording surface. This is in contrast to the conventional recording needles that record motor unit action potentials, which represent the synchronous depolarization of many adjacent muscle fibers. Based on the recording of the evoked action potential from one muscle fiber, the time variation in neuromuscular transmission for that fiber (jitter) can be determined. The test is based on the fact that the time variation for neuromuscular transmission (or latency from stimulus to action potential) is virtually constant for that muscle fiber with repeated measurements. Any alteration in NMJ transmission is likely to result in increased variation in the time of NMJ transmission. The test can be performed by one of two methods:

- The latency from the time of stimulus to the peak of an action potential for a single muscle fiber can be recorded repeatedly. The jitter value is then calculated by determining the mean value of the consecutive differences in latency (Fig. 14.9). In normal patients the latency is virtually constant.
- The interval between the evoked action potentials for two different muscle fibers from the same motor unit (interpositional latency) can be measured

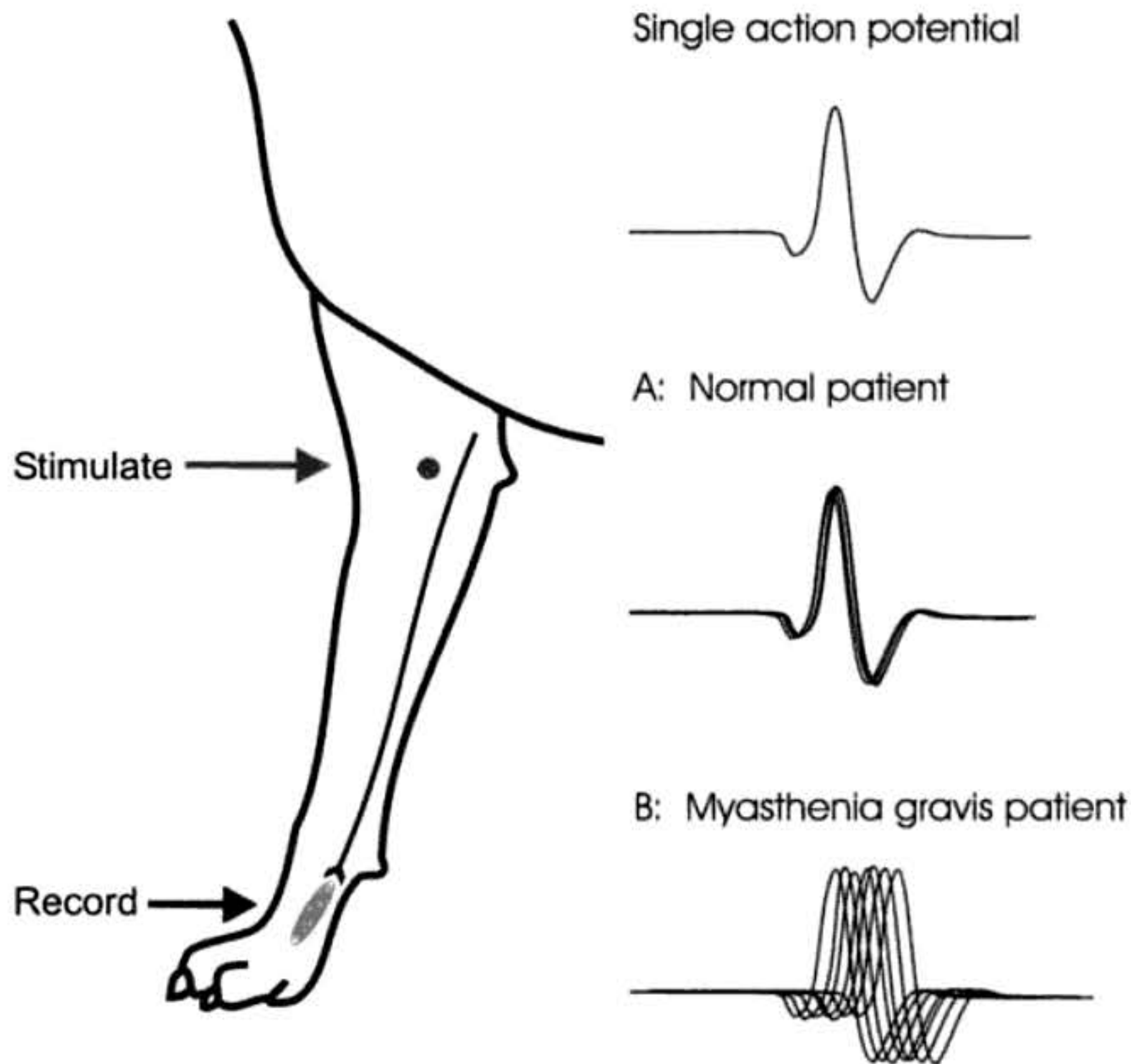


Fig. 14.9. Single fiber electromyography from a normal (A) and myasthenic (B) patient illustrating the increased variation in latency (jitter) occurring with MG.

repeatedly. The jitter value is the mean value of the consecutive differences in interposital latency.

The test is not specific for MG as any disorder of NMJ transmission may result in an abnormal jitter result. However the main contribution to jitter is impulse conduction at the synaptic cleft-end-plate region of the NMJ and in human medicine this test is therefore considered to be the most sensitive for detecting generalized MG and is still very sensitive in focal forms. A method for determining jitter has been reported in dogs, but use of the test in the diagnosis of MG has not been reported in veterinary practice to date.

Demonstration of elevated anti-ACh receptor antibody concentrations

The definitive diagnosis for acquired MG is made by demonstrating circulating antibodies directed against nicotinic ACh receptors of skeletal muscle, with the highest antibody concentrations generally occurring in cases with

acquired MG. Pretreatment with immunosuppressive drugs may decrease the chance of a positive test.

4. Treatment of myasthenia gravis can be subdivided into supportive treatment, which is similar for all cases with neuromuscular blockade, and specific therapy aimed at relieving the NMJ blockade and controlling the underlying autoimmune process in acquired MG.

Supportive treatment

Aspiration pneumonia

Prevention and/or treatment of aspiration pneumonia is important due to the increased morbidity and mortality associated with its development. Recumbent patients should be turned frequently (every 2 to 4 hr) to prevent hypostatic lung edema and exacerbation of any existing pneumonia. If aspiration pneumonia is present, or the development thereof is thought to be likely, then antibiotic therapy should be implemented. Ideally, the choice of antibiotic should be based on culture and sensitivity results from tracheal wash fluid and should be tailored to avoid using antibiotics associated with NMJ blockade. Frequent nebulization and coupage are useful in the treatment of pneumonia.

Fluid requirements

The maintenance of hydration in the face of significant regurgitation can be a challenge, especially as some animals tend to regurgitate liquids more readily than solids. Maintenance of fluid requirements with intravenous fluid therapy should be initiated if required.

Nutritional support

Maintenance of dietary intake is important in recumbent patients and particularly those with dysphagia or regurgitation. Elevated feeding may help in some cases with megaesophagus, but maintaining head elevation is difficult in cats. In those patients in which elevated feeding is undertaken, determining the ideal food consistency for that individual case is a matter of trial and error. Solid food stimulates pharyngeal and esophageal peristalsis more effectively in the normal dog, but some dogs with pharyngeal and esophageal dysfunction tolerate semisolid food better. The head should be maintained elevated throughout feeding and for 10 to 15 min following feeding. In those cases with unmanageable regurgitation, a nasogastric, pharyngostomy, or, ideally, a gastrostomy tube can be placed. Due to poor esophageal function, regurgitation can still occur with a nasogastric or pharyngostomy tube, and a gastrostomy tube would be better suited to MG patients. The advantages of gastrostomy tube placement include that head elevation during feeding is no longer required, the risk of aspiration pneumonia is reduced, and proper

delivery of oral medication can be guaranteed (versus variable delivery and passage time with megaesophagus and dysphagia). The disadvantages of gastrostomy tube placement are that only semiliquid and liquid foods can be administered and tube placement requires a short general anesthetic that may be deleterious to some myasthenics.

Respiratory support

Intensive care and specifically respiratory support may be required in animals demonstrating severe weakness.

Drugs to modify gastrointestinal tract function

The main consideration in the manipulation of gastrointestinal tract (GIT) function in MG is the management of megaesophagus and dysphagia, with the resultant complications of regurgitation, esophagitis, and aspiration pneumonia.

Improving esophageal motility

Drugs with prokinetic effects on GIT smooth muscle include metoclopramide and cisapride. Both of these drugs are believed to mediate their prokinetic effect by stimulating enteric cholinergic neurons, which in turn leads to ACh release and resultant smooth-muscle contraction. There is, however, no evidence that either of these two drugs stimulate increased esophageal motility in either the normal or MG-affected canine esophagus. Cisapride has actually been demonstrated to increase esophageal transit time in the normal dog. The dose of metoclopramide in the dog is 0.2 to 0.5 mg/kg given orally, intramuscularly, or subcutaneously every 8 hr and that of cisapride is 0.1 to 0.5 mg/kg given orally every 8 hr.

Increasing lower esophageal sphincter tone

Where elevated oral feeding is being used, drugs that increase lower esophageal tone should be avoided as this would result in resistance to the passage of food into the stomach. Increased lower esophageal tone would be beneficial where feeding is being performed via a gastrostomy tube by decreasing gastroesophageal reflux and consequently reducing or limiting esophagitis. Both metoclopramide and cisapride increase lower esophageal tone, with cisapride having the more potent action.

Prevention and management of esophagitis

Animals with megaesophagus and gastric reflux into the esophagus are at risk of developing esophagitis, which may in itself perpetuate esophageal dilation. The risk of esophagitis (or management thereof where esophagitis is already present) can be decreased by feeding via a gastrostomy tube (combined with drugs to increase lower esophageal sphincter resistance) and by increasing the pH of GIT content.

the severity of the autoimmune response against the ACh receptors may explain the variability to anticholinesterase therapy, as anticholinesterase therapy does not address the underlying autoimmune process. The effect of anticholinesterase therapy on improving esophageal function in dogs with megaesophagus is thought to be less than the effect on appendicular muscle weakness.

Immunosuppressive therapy

The use of immunosuppressive therapy in acquired MG is based on the underlying pathophysiology, an autoimmune destruction of functional ACh receptors. There is, however, some controversy about the use of immunosuppressive therapy in MG, with the main reasons being the high incidence of aspiration pneumonia in MG (especially in canine patients) with the potential for immunosuppressive therapy to exacerbate that, as well as the potential for glucocorticoid therapy to worsen neuromuscular weakness.

Glucocorticoid therapy

The potential for glucocorticoid therapy to exacerbate muscular weakness has been demonstrated in both dogs and cats, especially in cases with marked muscular weakness and respiratory distress. Increased muscle weakness associated with glucocorticoid therapy has been observed in 50% of human MG patients, as well as in dogs and cats. In one study of myasthenic cats, however, there was no demonstrable muscular weakness associated with glucocorticoid therapy. Some dogs (especially in the young age group) may go into spontaneous remission, even without immunosuppressive therapy. In cases responsive to edrophonium chloride, a conservative treatment regime would be to start pyridostigmine bromide therapy, combined with alternate-day low-dose (anti-inflammatory dose) prednisone therapy. Increasing (or in naïve cases introducing) corticosteroid therapy should be considered if the response to anticholinesterase therapy is suboptimal or if the animal is demonstrating resistance to the drug therapy. An initial dosage of 0.5 mg/kg body weight, every 12 hr is suggested in these cases, as higher doses may result in exacerbation of neuromuscular weakness. In cats, prednisone doses of 1 to 4 mg/kg/day have been used and dexamethasone at 0.25 to 2.0 mg/kg/day. Dexamethasone is associated with more gastrointestinal side effects and a higher myopathic potential than prednisone, and its use should therefore be avoided in MG. The exact mechanism whereby prednisone results in improvement of the clinical signs of MG is not fully understood, but may be related to inhibitory effects of prednisone on the formation and release of inflammatory agents, lymphocyte division, lymphocyte reactivity to ACh receptors, and leukocyte chemotaxis.

Azathioprine

Azathioprine is a cytotoxic antimetabolite that interferes with DNA synthesis, with its beneficial effect in acquired MG probably being mediated through

reducing lymphocyte numbers and consequently immunoglobulin production, as well as specifically inhibiting T-cell production. The use of azathioprine alone or combined with prednisone has been demonstrated to be highly effective in resolving clinical signs in human MG. Potential side effects of azathioprine therapy include the development of bone marrow suppression and, less often, hepatotoxicity, pancreatitis, and gastrointestinal tract irritation. Bone marrow suppression is much more common in cats and azathioprine use is therefore not advised in this species.

In dogs with evidence of bone marrow suppression (leukopenia with or without anaemia and thrombocytopenia), azathioprine therapy should be discontinued (or reduced in cases with mild bone marrow suppression). It is recommended that azathioprine be discontinued if the patient's white blood cell count is less than 4000 cells/ μ l, and/or if the neutrophil count is below 1000 cells/ μ l. The onset of clinical effect of azathioprine is delayed in both human cases and in dogs, and its use should therefore be combined with prednisone if an early effect is required. A conservative prednisone dose should be used initially, as discussed earlier. The clinical signs should abate rapidly with prednisone therapy. After 2 to 4 mo, the prednisone therapy can be tapered to a minimum alternate-day dosage or in some cases stopped entirely. This protocol should minimize side effects with rapid and sustained control of the clinical signs in many patients. In stable MG dogs, azathioprine may be considered as a sole immunosuppressive agent. It may take several weeks before an obvious clinical benefit is realized in such patients. The dose of azathioprine in dogs is 2 mg/kg body weight, divided into two daily doses 12 hr apart. Bone marrow function should be monitored by assessing for suppression on a hemogram every 1 to 2 wk during the initial 1 to 2 mo of therapy and every 1 to 2 mo thereafter.

Cyclosporine and cyclophosphamide

Both cyclosporine and cyclophosphamide have been demonstrated to have some efficacy in human cases of acquired MG, however their use in veterinary medicine is likely to be limited. Although its specificity for lymphocytes is an attractive feature, cyclosporine is extremely expensive. Cyclophosphamide is associated with more frequent and more severe side effects in comparison with other immunosuppressive drugs.

Mycophenolate mofetil (MMF)

Successful treatment of MG in a dog with mycophenolate mofetil (CellCept⁷, Roche Pharmaceuticals), an immunosuppressive drug with relative specificity for lymphocytes, has been reported. Institution of MMF therapy resulted in rapid resolution of clinical signs (within the first week of therapy) and return of the ACh receptor antibody concentration to within the normal range. The initial oral (or gastrostomy tube) dose of MMF is 20 mg/kg body weight, every 12 hr. Side effects of MMF in dogs are primarily gastrointestinal (e.g., vomiting, bloody diarrhea). It is recommended that the MMF dose be

reduced by half, once clinical signs of MG improve substantially or resolve, in order to minimize adverse side effects.

Intravenous immunoglobulin and plasmapheresis

Both intravenous immunoglobulin and plasmapheresis (plasma exchange) therapy have been demonstrated to be effective, although short-term, treatments for human acquired MG, particularly in acute fulminating MG where rapid improvement in the clinical signs is required. These techniques are limited in veterinary medicine due to the cost limitations and equipment requirements, but may be of benefit in the management of acute fulminating MG.

The mode of action of intravenous immunoglobulin is poorly understood but may be related to binding of circulating autoantibodies, blocking macrophage and lymphocyte Fc receptors, enhanced suppressor T-cell activity, and inhibition of the complement cascade. This therapy has been shown to be useful in the management of human acquired MG with few side effects but has not been assessed in the management of canine acquired MG.

Plasmapheresis involves removing the plasma and plasma constituents (including immunoglobulins) from whole blood of patients and returning the blood elements with either stored plasma or plasma substitutes to the patients. Immunoabsorption therapy is a form of plasmapheresis in which a patient's plasma is returned after being passed through a filter that adsorbs immunoglobulins. Plasmapheresis results in the removal of ACh receptor antibodies from circulation and has been shown to be effective with few side effects in human MG cases and in one dog with acquired MG, where its use was combined with prednisone therapy.

Management of concurrent neoplasia

If a concurrent thymic mass or other neoplasia is present, then surgery (with or without radiation therapy) should be considered. Removal of thymic hyperplasia has been demonstrated to improve remission rates in human patients with acquired MG. In contrast to the removal of thymic hyperplasia, thymoma removal in human patients with acquired MG is usually not associated with an improvement in clinical signs. Occasionally, a myasthenic person will worsen following thymoma removal. The improvement documented in human cases with thymic hyperplasia is probably related to the removal of a source of continued antigenic stimulation, while the worsening of the clinical signs occasionally seen in acquired MG following thymoma removal may be related to the loss of an immunosuppressive effect of the thymus.

The beneficial effect of thymic removal in the absence of a thymoma has not been demonstrated in dogs and cats. Thymic hyperplasia has also not been described in dogs and cats with MG and thymectomy in the absence of a demonstrable thymic mass would not be recommended due to the detrimental and stressful effects of surgery and anesthesia. In the few documented cases in which thymoma was performed in dogs with acquired MG, the outcome was generally poor, with all cases presenting with megaesophagus and

the majority dying of aspiration pneumonia shortly after surgery. It may therefore be prudent to avoid thymoma removal in myasthenic dogs or at least delay surgery until the clinical signs have first been adequately controlled with medical management. Successful management of thymoma with radiation therapy has been reported in a dog.

Treatment of acute fulminating myasthenia gravis

The mortality associated with MG is highest with the fulminating form, although luckily this is the most uncommon form of the disease. Cases present with rapidly progressive generalized weakness; rapid diagnosis and treatment (combining anticholinesterase therapy and ventilatory support) are therefore essential. The main cause of death in these cases is respiratory failure secondary to muscular weakness, and this may be further complicated by aspiration pneumonia. Care should be taken when initiating immunosuppressive therapy with corticosteroids, due to the potential to exacerbate the muscular weakness. In human cases with acute fulminating MG, plasmapheresis and intravenous immunoglobulin have been used but their use in veterinary medicine is limited by cost and availability.

Contraindications

Drugs that adversely affect NMJ transmission should be avoided, including ampicillin, aminoglycoside antibiotics, anti-arrhythmic agents, phenothiazines, anesthetics, narcotics, and muscle relaxants. Organophosphates may act in an additive manner with pyridostigmine and their concurrent use should therefore be avoided.

Prognosis

The overall prognosis for acquired MG in dogs is guarded due to this species' propensity to develop megaesophagus and aspiration pneumonia. The prognosis for recovery from acquired MG in dogs is good if severe aspiration pneumonia or pharyngeal weakness is not present. In humans, the prognosis with uncomplicated acquired MG is considered good to excellent. However, the incidence of aspiration pneumonia in canine patients is significantly higher than in human medicine and the overall survival rate is therefore lower than human patients. The overall one-year mortality rate for canine acquired MG has been reported to be between 40% and 60%. The reason for death or euthanasia of myasthenic dogs is almost always severe or recurrent aspiration pneumonia. In order to maximize the chance of a favorable outcome in canine MG patients, aggressive prevention and/or treatment of aspiration pneumonia is essential.

Information on documented cases of acquired MG in cats suggests that the prognosis for focal and generalized MG may be better than that reported for dogs. This is likely due to the lower incidence of megaesophagus and associated aspiration pneumonia in cats. In one series of acquired MG in 20 cats, only 3 of the cats died and all 3 of these presented with acute fulminating

MG with death due to respiratory failure. Of the remaining cats, 11 of 20 demonstrated improvement of clinical signs at 2 mo after diagnosis, with 6 remaining unchanged. One-year follow-up was available for 5 cats, at which time 2 were still alive, while the other 3 cats had died or were euthanized for unrelated illnesses. At one and a half years, 2 cats were found to be free of clinical signs of disease.

Clinical remission of MG is associated with a return of serum ACh receptor antibody concentrations to the normal range. These concentrations should therefore be evaluated every 6 to 8 wk to monitor the clinical course of the disease.

VI. Drugs and Toxins Associated with Junctionopathies (see Table 14.2)

A. Algae-derived toxins⁷⁴⁻⁸⁰

1. Blue-green algae (anatoxins)

Anatoxin- α has been isolated from at least three genera of freshwater cyanobacteria (blue-green algae) and has been demonstrated to be a bicyclic secondary amine. The offending blue-green algae genera include *Anabaena*, *Aphanizomenon*, and *Oscillatoria*. Anatoxin- α (s) has been isolated from *Anabaena flos-aquae*, which is distinct from the *Anabaena* strains that produce anatoxin- α . Anatoxin- α (s) is a naturally produced organophosphate that has been responsible for a variety of animal poisonings, including dogs. Anatoxin- α (s) has been demonstrated to be a potent irreversible inhibitor of ACh in experimental studies and certainly the inhibitory kinetics of anatoxin- α (s) are supportive of an in vivo anticholinesterase action. Anatoxin- α (s) toxicity can be reversed by treatment as for cholinesterase toxicity, including the use of oxime reactivators, carbamates, and atropine.

2. Green algae (charatoxin)

Charatoxin is produced by the alga *Chara globularis*, which has been shown to be an insecticidal agent. In high concentrations it is a competitive antagonist at the nicotinic ACh receptor, while at lower concentrations it enhances ACh binding.

B. Antibiotics^{10,81-112}

Antibiotics causing NMJ blockade are unusual in veterinary medicine, but the understanding of the few reported cases is augmented by the large amount of experimental data. One of the most important areas of concern is the concurrent use of these antibiotics and anesthesia incorporating NMJ blocking agents or in animals with concurrent MG. Certainly, gentamycin has been shown to augment the neuromuscular blockade of atracurium in anesthetized horses. Antibiotics with demonstrated NMJ blocking effects include:

- Aminoglycosides
- Lincomycin
- Penicillamine

- Polymyxins
- Tetracyclines

Table 14.2: Drugs and Toxins Associated with NMJ Blockade Syndromes

Algae:

- Blue-green algae (anatoxins)¹*
- Green algae (charatoxin)

Antibiotics:

- Aminoglycosides*
- Lincomycin
- Penicillamine (penicillin degradation product)
- Polymyxins*
- Tetracyclines

Antiprotozoal agents:

- Chloroquine
- Quinine

Black widow spider venom

Botulinum toxin

Gila Monster venom

Hornet Mandaratoxin (*Vespa mandarinia*)

Interferon α

Lithium

Marine toxins

Methoxyflurane

Neuromuscular blocking agents:

- Hexamethonium
- Succinylcholine
- Trimethaphan Camsylate
- Vecuronium

Pesticides:

- Organophosphorus compounds*
- Carbamates

Poisonous plants

- Delphinium* spp. (larkspur)
- Dihydro- β -erythroidine (alkaloid from seeds of the genus *Erythrina*)
- Hemlock (*Conium maculatum*)
- Tubocurarine (*Strychnos toxifera*)

Snake venoms

Tetanus toxin (minor effect)

Tick bite paralysis

Note: Includes experimental and human drugs and toxins.

¹Italic type indicates clinically most important agents and syndromes except the scientific genera and species names.

Of these, the aminoglycoside antibiotics are clinically the most important.

1. Aminoglycoside antibiotics

The aminoglycoside family of antibiotics is primarily used to treat infections from aerobic gram-negative bacteria. These drugs act in a bactericidal manner by interfering with protein synthesis. The family includes gentamycin, neomycin, streptomycin, kanamycin, tobramycin, amikacin, and netilmycin. The primary limitations for the use of aminoglycoside antibiotics are the development of ototoxicity and nephrotoxicity, but acute neuromuscular blockade has been reported, particularly when aminoglycoside antibiotics are used in conjunction with general anesthesia.

The toxic mechanism for the acute, reversible NMJ blockade induced by aminoglycoside antibiotics appears to be mediated via calcium antagonism at the external cell membrane channel sites on both the presynaptic and postsynaptic cell membrane. The NMJ blockade induced by aminoglycoside antibiotics is transient and experimentally is virtually completely antagonized by calcium and partially antagonized by neostigmine. All members of the aminoglycoside family can cause NMJ blockade, but both the degree of NMJ blockade and the balance between pre- and postsynaptic effects vary between the different agents. In order of decreasing effect of NMJ blockade are neomycin, kanamycin, amikacin, gentamycin, and tobramycin.

Presynaptic inhibition of NMJ transmission, by the inhibition of ACh release, is a feature of all aminoglycoside antibiotics. With gentamycin, the presynaptic NMJ blockade has been demonstrated to be as a result of extracellular blockade of calcium influx. Neomycin has been demonstrated to be the aminoglycoside antibiotic with the most potent presynaptic NMJ blocking effect; this presynaptic block of ACh release by neomycin is so predictable that it has been used experimentally to reverse organophosphorous anticholinesterase-induced NMJ blockade.

The difference between members of the aminoglycoside family lies in the varying degree of effect on postsynaptic NMJ blockade and this may in part be due to the effect being mediated via two different mechanisms. Neomycin displays significant postsynaptic NMJ blockade by apparently interacting with the ion channel receptor in the open configuration and is partially reversible by neostigmine. The effect of streptomycin on the postsynaptic NMJ is minimal and is mediated by blocking the receptor, and neostigmine causes minimal reversal.

Reports of aminoglycoside toxicity causing NMJ blockade are limited in veterinary medicine and mainly made up of experimental studies, particularly in cats. One animal was reported that developed severe muscle weakness and hyporeflexia following five days of gentamycin therapy for deep pyoderma and in which the clinical signs resolved 48 hr after the antibiotic was withdrawn. The onset of NMJ blockade is rapid, and in severe cases may progress from weakness to tetraplegia with respiratory paralysis within four to six hours. Reported aminoglycoside NMJ blockade in humans is most common in the

presence of concomitant disease of the NMJ (e.g., MG) or concomitant administration of NMJ blocking agents (e.g., succinylcholine), but occasional cases do occur in the absence of predisposing factors. In human medicine, it appears that a high dose of aminoglycoside antibiotic is not always required and that the duration of medication prior to the development of clinical signs is variable. Certain predisposing factors that have been recognized include:

- The intravenous, intraperitoneal, and intrapleural routes of administration are more risk-prone as are high doses rates.
- Impairment of renal excretion through renal disease or dehydration increases the risk.
- Some other disease states increase the risk, particularly gram-negative septicemia.

Treatment of aminoglycoside-induced NMJ blockade is by withdrawal of the antibiotic therapy, which is usually followed by rapid recovery as the plasma aminoglycoside levels decline. In patients with impaired renal function, fluid therapy may be required. In human patients, calcium chloride and neostigmine have been administered, with variable success, usually in an attempt to reverse NMJ blockade in emergency postanesthetic situations.

2. Lincomycin

Lincomycin is produced by an actinomycete, *Streptomyces lincolnensis*, but has largely been supplanted by clindamycin, which is more active and has fewer side effects. The mechanism of lincomycin action on the NMJ probably involves both pre- and postsynaptic mechanisms. There are no veterinary reports of lincomycin-induced NMJ blockade and the reports in human medicine are largely confined to the potentiation of effects of *d*-tubocurarine and pancuronium.

3. Penicillamine

Penicillamine is a degradation product of penicillin and the D-isomer is an effective chelator of copper, zinc, mercury, and lead. It is used in human medicine as a chelating agent for the treatment of cystinuria (by forming a soluble disulphide compound with cysteine) and for the suppression of rheumatoid arthritis. Penicillamine is not routinely used in veterinary medicine; however in human medicine the neurotoxic effects include the induction of MG and polymyositis/dermatomyositis.

Penicillamine induces MG in up to 7% of human patients and appears to act by altering the antigenic structure of the ACh receptor and subsequently initiating a new autoimmune response.

4. Polymyxins

The polymyxin antibiotics, comprising polymyxin B and polymyxin E, are microorganism-derived polypeptides that disrupt the structure of cell membranes and are effective against gram-negative bacteria. There is no absorption through mucous membranes and enteral administration does therefore not result in systemic effects. Following parenteral administration,

Clinical signs of black widow spider evenomation in human medicine are a reflection of hyperactivation of motor, sensory, and autonomic sympathetic systems. The motor clinical signs include tremor, spasmodic leg movements, and clonic muscle contractions. This is followed by the development of flaccid paralysis. Sensory clinical signs include the development of intense generalized pain and hyperesthesia and abdominal pain and rigidity. Salivation, lacrimation, sweating, and tachycardia frequently accompany these clinical signs. Reports of veterinary black widow spider evenomation are rare, but have been recognized for a number of years. It has been reported that the cat appears more susceptible to black widow spider evenomation. In one report of apparent evenomation in a cat, the presenting clinical signs were very similar to those seen in human medicine. The affected cat demonstrated progression from fine-muscle tremors, muscular spasticity, abdominal pain with a rigid abdomen, and an increased respiratory rate to profound muscle weakness and flaccidity. Electrolyte disturbances in the case included a profound hypocalcemia and hypokalemia. Within two hours of antivenin administration, a clinical improvement characterized by an improvement in respiratory function and a return to sternal recumbency was evident.

Treatment of black widow spider evenomation is based on administration of antivenin and correction of electrolyte disturbances, particularly any existing hypocalcemia. As the antivenin is equine derived, sensitivity testing by administering a small intradermal test dose prior to administering the parenteral dose is essential. A rapid response is usually seen following administration of the antivenin. In human medicine, the clinical signs associated with untreated spider bites usually subside after 48 to 72 hr. Further supportive treatment, including maintenance of fluid balance and analgesia, should be considered. Due to the reported potential for cardiovascular arrest in young or elderly patients in human medicine, consideration should be given to blood pressure monitoring in veterinary cases.

E. Botulinum toxin (botulism)^{10,16,132-144}

1. Botulism is the term used to describe the disease caused as a result of ingestion of preformed *Clostridium botulinum* exotoxin. Botulism toxin is one of the most potent known toxins. The usual cause of botulism is ingestion of toxin in uncooked and spoiled food (in dogs, most frequently raw meat) or carrion, but in rare cases botulism may occur as a result of gastrointestinal (GIT) formation of botulism toxin secondary to colonization of the GIT tract with the "toxico-infectious" form of *Clostridium botulinum*. Preferential colonization sites for *Clostridium botulinum* appear to be the GIT and liver wounds (ulcers and abscesses).

Eight types of botulinum toxin have been identified based on differing antigenic properties, including A, B, C₁, C₂, D, E, F, and G. The majority of human cases are associated with types A, B, and E, while in veterinary medicine most cases are caused by types C and D. In dogs the most common toxin associated with clinical disease is type-C₁, although two cases of type-D intox-

ication have been reported from Senegal. Type-C₂ botulinum toxin is not considered to be neurotoxic, although it may alter vascular permeability. Botulism is uncommon in the dog, while in cats no naturally occurring cases have been reported; however, the disease has been experimentally reproduced in cats. Type-C botulism has been reported in lions. The botulinum toxins are serologically distinct, but the majority result in similar neurotoxic effects.

The main effect of botulinum toxin is to block the release of ACh at the level of the NMJ and at cholinergic autonomic synapses. This results in the development of flaccid paralysis and alterations in the autonomic nervous system. The botulinum toxin is absorbed from the stomach and upper small intestine following ingestion of food containing the preformed toxin (or local production in the toxico-infectious form). Type-E toxin appears to be activated and made more potent by the proteolytic enzymes in the upper GIT, although in the other toxin types there is evidence that some of the toxin does get denatured. Toxin passing through to the lower GIT demonstrates lower absorption efficiency. Once absorbed, the toxin passes into the general circulation, where it circulates to cholinergic synapses in the peripheral nervous system, including the NMJ, followed by binding of the toxin to receptor molecules on the external surface of the cell membrane. The receptor is postulated to be sialic acid to which rapid bindings occurs, independent of neural activity and temperature. The toxin is then internalized into the nerve terminal within a vesicle. Internalized toxin is not accessible to neutralization by antitoxin. The toxin inhibits neurotransmitter release by cleaving the proteins required for neurotransmitter exocytosis.

2. Onset and severity of clinical signs are dependent on the total dose of toxin ingested and typically develop rapidly within 12 hr (up to six days) following ingestion. Affected animals develop a progressive and symmetrical paresis, progressing to flaccid paralysis that typically first becomes evident in the pelvic limbs before extending to the thoracic limbs. Consistent with a lower motor neuron lesion, reflexes and muscle tone are decreased to absent. In severe cases, death may result from paralysis of the respiratory muscles. Sensory function, including pain perception, and level of consciousness are unaffected. Distinct from other causes of diffuse lower motor neuron signs, with botulism there is frequently additional evidence of cranial nerve deficits (e.g., facial nerve paralysis, depressed gag reflex, decreased jaw tone, and megaeosophagus) and occasional evidence of dysfunction of the cholinergic neurons of the autonomic nervous system. The cholinergic signs include alterations of heart rate (elevated or decreased), pupil changes (mydriasis with depressed pupillary light reflexes), keratoconjunctivitis sicca, urinary retention, and constipation.
3. Diagnosis of botulism is primarily based on the history and suggestive clinical presentation. Due to the dietary origin of the toxin, multiple cases may occur in some situations. Routine laboratory analysis is usually unremarkable and the definitive diagnosis is based on the demonstration of botulinum toxin

early in the course of the disease, either in blood (10 ml of serum should be collected) or GIT contents (50 g of feces, vomitus, or food sample should be collected). It is essential to discuss the diagnostic sample requirements with the laboratory performing the investigation. Electrodiagnostic evaluation may assist in the diagnosis but is not definitive. Affected cases may demonstrate decreased amplitude of compound evoked muscle action potentials. Repetitive nerve stimulation at low frequency rates (e.g., less than 5/sec) may produce a small decrement in compound muscle action potentials; rapid rates (e.g., 50/sec) are likely to produce an increment in successive compound muscle action potentials. Electromyography may demonstrate fibrillation potentials and positive sharp waves after 7 to 10 days of paralysis. Motor nerve conduction velocity may be decreased but is usually unaffected.

4. Treatment of botulism toxicity is largely supportive as toxin internalized into the nervous system is not accessible to antitoxin. As in any recumbent animal, the prevention of pressure sores by maintaining patients on soft surfaces (padded mattresses or water beds) is important as is the provision of fluid and dietary requirements (by intravenous fluid administration and nasogastric, pharyngostomy, or gastrostomy tube placement in more severe cases). In the presence of megaesophagus and a decreased gag reflex, special care must be taken to minimize the potential for the development of aspiration pneumonia, in the event of which prompt antibiotic therapy, combined with coupage and nebulization, should be initiated. Antibiotics with the potential to interfere with NMJ transmission should be avoided (e.g., aminoglycosides).

Due to the potential for autonomic dysfunction, close attention should be paid to bladder and bowel function, with suitable intervention if required. Botulism toxicity is the result of ingestion of preformed toxin and covering antibiotic therapy is therefore not indicated in the absence of secondary bacterial infections. Due to the relative inaccessibility of the bound botulinum toxin, administration of antitoxin (if available) should only be considered in severe cases and if toxin exposure occurred relatively recently (within 5 days), and then only following a negative response to an intradermal test dose to avoid anaphylaxis. The polyvalent antitoxin, containing type-C antitoxin, is indicated in dogs. Mild to moderately affected dogs should recover spontaneously in the absence of pneumonia. Affected animals do not usually develop immunity to future episodes as the dose of toxin sufficient to cause clinical signs is not usually sufficient to stimulate a protective immune response. Prevention of repeat episodes (although extremely rare) is based upon preventing access to preformed toxin in the diet by limiting access to carrion and not feeding raw or contaminated meat. Botulism toxin can be neutralized by heating food to 100°C for 10 min or 80°C for 30 min.

F. Gila monster venom^{129,145-147}

The Gila monster (Mexican bearded lizard—*Heloderma horridum horridum*) is a nocturnal reptile living in arid regions of southern North America. Gila monsters

may bite following provocation and the painful bite is always associated with the injection of toxin B comprised of a variety of toxins. Neuromuscular junction (NMJ) blockade syndrome is reported as one of the syndromes of *Gila* evenomation in human medicine, but is more likely to be the consequence of hypotension due to vasoactive effects of a kallikrein-like enzyme and not primary neurotoxin effects on the NMJ. Treatment is supportive, with no specific antivenin being available.

G. Hornet mandaratoxin¹⁴⁸

Experimental studies on mandaratoxin from the hornet (*Vespa mandarinia*) have shown that it induces irreversible blockade of the excitatory postsynaptic potential of the NMJ.

H. Interferon- α ^{149,150}

The potential neurotoxic effects of interferon- α are relevant now that its use is increasing in veterinary medicine. In human medicine, myasthenia gravis secondary to interferon- α therapy has been reported in nine patients. It appears that interferon- α results in induced autoantibodies against the ACh receptors in the postsynaptic membrane and may require pyridostigmine therapy.

I. Lithium^{153,154}

In experimental studies on dogs, lithium has been demonstrated to significantly prolong NMJ blockade with both pancuronium bromide and succinylcholine. Although the NMJ blocking effects of lithium are well documented, the exact toxic mechanism is unclear.

J. Marine toxins¹⁵¹

Marine toxins with demonstrated NMJ blocking effects include:

- Greenland shark meat (*Somniosus microcephalus*): α -Glycerotoxins— toxin from polychaete annelid worms *Glycera dibranchiata* and *G. convoluta*
- Holothurinas and holotoxins—saponin toxins from sea cucumbers (*Holothuri- oidea*)
- Lophotoxin—toxin from Pacific soft (gorgonian) corals (sea fans and whips of the *Lophogorgia* spp.)
- Marine cone snails (Conotoxins)
- Nereistoxin and related toxins (marine worm—*Lumbriconereis heteropoda*)
- Sea snakes
- Stonefish (*Synanceja horrida*) venom

Considering the environment these organisms normally inhabit, dog and cat evenomation would be extremely unusual. For example, human evenomation by the fish-hunting marine cone snails (Conotoxin) is almost exclusively restricted to

sponge divers. Reported veterinary exposure is confined to sea snakes and Greenland shark meat.

Ingestion of meat of the Greenland shark (*Somniosus microcephalus*), particularly fresh meat, has been demonstrated to be toxic to both humans and dogs. Toxin analysis has demonstrated high levels of trimethylamine oxide, which is reduced in the gastrointestinal tract to trimethylamine (TMA). TMA toxicity occurs acutely following consumption of Greenland shark meat. In experimental studies, low doses result in increased NMJ contraction, while high doses appear to cause NMJ blockade.

K. Methoxyflurane¹⁵²

Methoxyflurane has been reported to produce an apparently subclinical MG syndrome in a human anesthetist, but no veterinary or experimental studies are reported.

L. Neuromuscular blocking agents¹⁵⁵

These agents are categorized as follows:

- Membrane stabilizing agents, e.g., vecuronium
- Depolarizing agents, e.g., succinylcholine

The neuromuscular agents, of which *d*-tubocurarine was the prototype, are used clinically to induce NMJ blockade, usually as an adjunct to general anaesthesia.

Membrane stabilizing NMJ blocking agents

The curare-class of NMJ blocking agents act on the postsynaptic membrane, binding to the nicotinic cholinergic receptor and competitively blocking the action of ACh. These agents can be classified according to their duration of action into long-, intermediate-, and short-acting. *d*-Tubocurarine is an example of a long-acting agent (and also one of the most potent), atracurium and vecuronium are examples of intermediate-acting agents and mivacurium is an example of a short-acting agent. The development of newer agents allows a more rapid onset of action, as due to the fewer side effects of these newer agents (including histamine release, bronchospasm, hypotension, and excessive secretions) higher doses can be tolerated. Treatment of overdose or reversal of the effects following general anaesthesia is, in general, by administration of anticholinesterase agents (neostigmine, pyridostigmine, or edrophonium), muscarinic antagonists (atropine or glycopyrrolate) to prevent muscarinic stimulation, antihistamines to counter the antihistamine effects and sympathomimetics to maintain blood pressure.

Depolarizing NMJ blocking agents

In contrast to the stabilizing NMJ blocking agents of the curare class, the depolarizing NMJ agents (including succinylcholine and decamethonium) induce depolarization of the postjunctional membrane by opening ion channels, simi-

larly to ACh, but the resultant depolarization in the end plate and adjacent area of the sarcoplasmic reticulum is persistent.

Ganglionic-blocking agents

Muscle relaxants in clinical use that act as ganglionic-blocking agents may have similar clinical signs to the NMJ blocking agents. These substances inhibit synaptic transmission by blocking postsynaptic ion channels and include hexamethonium and trimethaphan camsylate.

M. Pesticides¹⁵⁶⁻¹⁶³

1. Organophosphorous compounds (organophosphates)

Organophosphorous (OP) compounds comprise around 20,000 different chemical formulations and represent one of the most widely studied groups of toxins. Clinical toxicosis with OP compounds in veterinary medicine is mainly restricted to those substances used as pesticides and usually following inappropriate or accidental dosing and overdosing. The neurotoxic effects of the OP compounds can be divided into a number of clinical categories, including:

- Cholinergic syndrome (muscarinic, nicotinic, and CNS effects)
- OP-induced delayed polyneuropathy
- Neuromuscular transmission syndrome (junctional myopathy)
- Chronic encephalopathy (cognitive dysfunction in affected humans)

Experimentally, the cholinergic dysfunction and the delayed peripheral neuropathy effects have been extensively studied. The NMJ effects are usually insignificant in relation to the other neurotoxic effects of OP compounds. The underlying pathology resulting in the neuromuscular transmission syndrome has been demonstrated for a number of anti-AChE agents, including several OP compounds, given at doses causing muscle fasciculation. The primary feature is the presence of a myopathy in selected skeletal muscles, with myofiber necrosis limited to the region of the NMJ and sparing the end-plate free regions of the muscle. The myopathy is limited to a small proportion of fibers in certain muscle groups. The necrosis in the region of the end plate suggests that the myopathy reflects alterations in the end plate induced by ACh esterase inhibition (Fig. 14.10), but the exact mechanism is not fully understood.

2. Carbamates

The carbamates are either carbamic or dithiocarbamic acids that are widely used as insecticides, fungicides, and herbicides. Neurotoxic effects of carbamates can be divided into two categories:

- Insecticides that have direct neurotoxic effects
- Fungicides that mediate their neurotoxic effects through their breakdown products

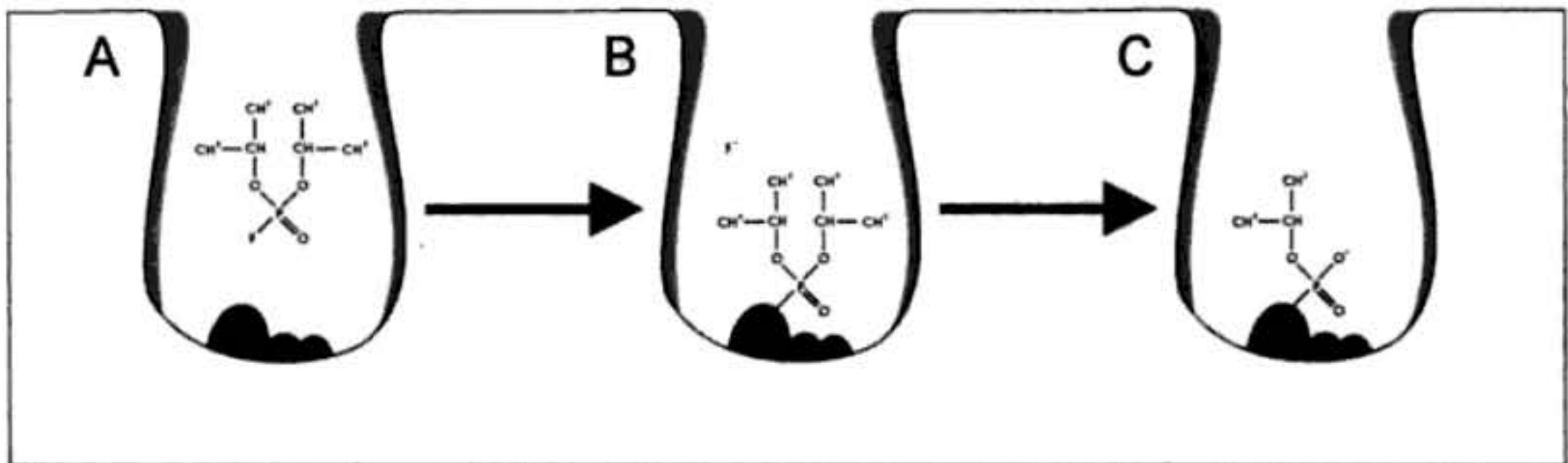


Fig. 14.10. Schematic representation of the interaction of organophosphorus compounds with the ACh esterase active center. Phosphorylation of the enzyme active site by organophosphorus compounds is similar to acetylation of ACh, but in contrast to ACh, the phosphorylated enzyme is stable (A and B). When aging occurs the enzyme becomes irreversibly inhibited (Modified from Lotti 2000, with permission¹⁵⁶).

Insecticide carbamates

The insecticidal carbamates are most widely used in veterinary medicine as flea and tick formulations. Toxicity due to insecticidal carbamates usually results in immediate mild to severe signs that rapidly resolve in most cases. In rare cases, neurologic signs may be delayed or prolonged. The carbamate insecticides target ACh esterase at parasympathetic autonomic junctions, all ganglia and NMJs. Additionally, carbamate insecticides may inhibit erythrocyte ACh esterase, plasma pseudocholinesterase, and tissue nonspecific carboxylesterase. Short-term exposure of dogs to repeated oral doses of carbamate insecticides does inhibit plasma, erythrocytic, and CNS cholinesterases, with associated typical clinical signs of cholinergic toxicity, but does not result in prolonged nervous system effects.

If carbaryl is used as an example of a typical carbamate insecticide toxicity, toxic signs would usually first become apparent after 15–30 min following administration, with peak clinical signs at 90 min to 4 hr. Clinical improvement should be apparent by 6 hr, and most of the clinical signs should resolve by 24 hr. Long-term administration is associated with the development of tolerance, with dogs receiving oral aldicarb for up to 2 yr demonstrating no toxic effects. Carbamate esters appear to induce some neurologic and behavioral changes at dose levels with minimal evidence of toxic effects and in the presence of normal nervous tissue ACh esterase activity. The most dramatic evidence of the effect of carbamate toxicity on the NMJ (in addition to other cholinergic effects) was demonstrated in experimental studies in pigs receiving oral carbaryl at 150 mg/kg body weight for up to 83 days. These pigs developed progressive MG, ataxia, intention tremor, and clonic muscular contractions leading to paraplegia and recumbency.

Treatment of carbamate insecticidal toxicity is primarily by removing the source and combating the excessive ACh effects by the administration of

picture. Livestock intoxication is much more common in North America (*Delphinium barbeyi*, tall larkspur; *D. andersonii*, low larkspur) than in Europe (*D. elatum* and *Consolida elatum*), where the *Delphinium* species appear to be less toxic. A number of factors determine toxicity, including plant species, growth stage, plant parts, soil composition, and climate.

2. *Aconitum* spp. (monkswood and aconite)

These plant species contain similar toxic alkaloids to those of the *Delphinium* species.

3. Dihydro- β -erythroidine (from genus *Erythrina*)

Dihydro- β -erythroidine is an alkaloid derived from seeds of trees and shrubs of the genus *Erythrina*, which has been demonstrated to be a competitive antagonist at muscle and neuronal nicotinic receptors. The NMJ effects can be partially reversed with neostigmine.

4. Hemlock (*Conium maculatum*)

The neurotoxic agent of *Conium maculatum* (hemlock, poison hemlock, spotted hemlock, Nebraska or California fern, or poison fools parsley) is responsible for occasional accidental livestock and rare human poisoning. The plant is widespread over Europe, Asia, and North and South America. The toxic agent, coniine, results in depression, muscular weakness, and death due to respiratory failure in laboratory animals and domestic herbivores. The exact mechanism of NMJ blockade is poorly understood, but the toxic agent has a curare-like action.

5. Tubocurarine (*Strychnos toxifera*)

The curare class of NMJ blocking agents was originally derived from the *Strychnos* species of plant, which are widespread throughout the world. The main neurotoxic agent, tubocurarine, acts on the postsynaptic membrane, binding to the nicotinic cholinergic receptor and competitively blocking the action of ACh. Following administration, the clinical signs rapidly progress from initial muscle weakness to flaccid paralysis. The first muscles to be affected are the small rapidly moving muscles (e.g., extraocular muscles), followed by the limb muscles, the intercostal muscles, and finally the diaphragm. Recovery occurs in reverse order to the loss of motor function. As tubocurarine (and related compounds) are unable to cross the blood-brain barrier, there are no central effects.

O. Snake envenomation^{129,173–179}

The following snake venoms are capable of causing NMJ blockade:

- *Bungarus fasciatus* (krait)—ceruleotoxin
- Cobra venom
- Coral snake (*Micrurus fulvius*) and Sonoran coral snake (*Micruroides euryxanthus*)
- *Crotalus durissus terrificus* (southern Brazilian rattlesnake)—crotoxin
- *Crotalus scutulatus scutulatus* (North American Rattlesnake) Mojave toxin
- Mamba snake toxin

mal test dose to minimize the risk of anaphylaxis. The antivenin is most effective if administered within three to four hours of envenomation. The venom of the Sonoran coral snake (*Micruroides euryxanthus*) is not inactivated by the *Micrurus fulvius* antivenin and the treatment in this case is largely supportive. Luckily this species of coral snake is less aggressive (bites are therefore less common) and the symptoms in human patients are also less severe. The dose of antivenin is based on an estimation of the amount of venom injected into the patient, but this is difficult in practice and a minimum of two vials should be administered. In a study assessing the efficacy of antivenin treatment on snakebite incidents in Australia (all types of venom, not just those acting against the NMJ), the administration of antivenin significantly improved the chances of survival in both dogs (from a survival rate of 31% to 75%) and cats (from a survival rate of 66% to 91%).

P. Tetanus toxin (minor effect)¹⁴⁴

In addition to the effect that tetanus toxin has on the inhibitory neurons in the CNS, resulting in release of spinal cord and brain-stem motor neurons from inhibition with subsequent hyperexcitability (Fig. 14.11), the toxin may also have a direct effect on the peripheral somatic neurons. It is thought that the toxin has a direct facilitatory effect at the neuromuscular junction of these neurons. This effect is believed to be mediated by the affinity for binding of hematogenously



Fig. 14.11. English Springer spaniel demonstrating the classical symptoms of generalized tetanus. In addition to the effect on inhibitory neurons in the CNS, tetanus toxin may also have facilitatory effects at the neuromuscular junction.

spread tetanus toxin to the NMJ, and this effect may be seen prior to the migration of tetanus toxin to the CNS. Canine and feline tetanus are discussed in detail in Chapter 13.

Q. Tick bite paralysis (tick paralysis)^{10,16,180–194}

1. A flaccid and afebrile ascending motor paralysis has been demonstrated in animals and people after exposure to a neurotoxin generated by some strains of certain tick species. Not all infested animals are affected, with cats in the United States appearing resistant. In Australia, infestation with the nymphs and larvae, and not only the adult tick, may result in clinical signs. The ticks release a salivary neurotoxin. The toxin acts by interfering with ACh release at the NMJ and/or propagation of the impulse along motor axon terminals. The toxin may affect both sensory and motor nerve fibers by altering ionic fluxes that mediate the production of the axon potential. Sixty-four tick species have been shown to have the potential to produce paralysis, but the species of clinical significance in the dog and cat population include:

- *Dermacentor variabilis* (common wood tick)—the most commonly incriminated species in North America
- *Dermacentor andersoni* (Rocky mountain wood tick)
- *Ixodes holocyclus*—the most commonly incriminated species in Australia
- *Ixodes cornuatus* and *Ixodes hirsti*—occasionally cause paralysis

Tick paralysis in Australia appears to result in much more severe clinical signs, frequently leading to death due to central nervous system effects and respiratory failure within one to two days if dogs are left untreated. Despite the relative frequency of livestock paralysis secondary to tick saliva in Southern Africa, NMJ blockade syndromes in dogs and cats secondary to tick saliva are rare. Paralysis in a dog secondary to the infestation by the hedgehog tick (*Rhipicephor nuttalli*) has been reported in this region.

The exact nature of the toxic agent in tick saliva is unknown and only gravid females of the ixodid species and larvae of the argasid species cause tick paralysis. Supportive of the toxic principle being in tick saliva are the following observations:

- The incubation period is constant, with disease progression mirroring the feeding habits of the respective tick species.
- Precise manipulation of the incubation period is possible by applying ticks that have been allowed to feed on other individuals.
- Clinical signs are usually only present when the ticks are fully engorged and rapidly resolve following removal of the ticks.
- Severity of clinical signs is closely correlated to severity of the tick infestation.

- Clinical signs of paralysis can be induced by administering tick saliva or tick homogenate to test animals.
 - NMJ blockade can be induced in nerve-muscle explants by administration of tick salivary gland isolates.
 - Inoculation of animals susceptible to tick paralysis with material from affected animals fails to induce paralysis.
2. Affected animals present with an acute, rapidly progressive flaccid paralysis with decreased to absent spinal reflexes. A range of 5–9 days of tick attachment is thought to be required for development of clinical disease. Quadriplegia often develops within 12–72 hr from the onset of clinical signs. Weakness usually first develops in the pelvic limbs and progresses to involve the thoracic limbs. Tendon (stretch) reflexes (e.g., patellar reflex) are typically lost before withdrawal reflexes. Cranial nerves are occasionally involved. Some dogs may exhibit a voice change (weak bark), suggesting laryngeal involvement. Facial and masticatory muscles may also be affected. Sensory function is unaffected. Urethral and anal sphincter function is also typically unaffected. In severe cases, death may result from respiratory failure or aspiration pneumonia.
3. Diagnosis is based on the history, suggestive clinical presentation, and identification of the offending tick species (in some cases the engorged female may have dropped off, so a negative finding does not exclude tick paralysis). As only one tick may cause the clinical signs, in some cases a careful search of the affected animal is required. Electrophysiological studies in human patients with *Dermacentor*-induced NMJ blockade have demonstrated:
- Motor neuropathy with decreased motor nerve conduction velocity
 - Decreased compound motor evoked muscle action potential amplitude in nerves and their corresponding muscles
 - Impaired afferent nerve impulse propagation
 - A requirement for higher nerve stimulus current in order to elicit a muscle response

Findings of electrophysiological studies in children with *Ixodes holocyclus*-induced NMJ blockade include:

- Decreased evoked compound motor muscle action potential amplitude
 - Normal motor nerve conduction velocity, normal sensory conduction and a normal response to repetitive stimulation
4. Identification and removal of the offending tick usually results in rapid recovery that may start within hours and continue over several days, although some cases may demonstrate persistent clinical signs for some weeks. In tick

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Chapter 15

NURSING CARE FOR PATIENTS WITH NEUROLOGIC DISEASE

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I. Introduction^{1,2}

Caring for patients with neurologic disease can be extremely challenging, especially if those patients are nonambulatory or only weakly ambulatory. Management of the recumbent dog or cat involves primarily supportive care. A treatment protocol should be implemented at the onset of paresis or paralysis in order to prevent or lessen the severity of complications such as pulmonary atelectasis or pneumonia, urinary bladder damage and urinary tract infections, decubital ulcers, muscle atrophy, joint stiffness, pain, inadequate nutritional intake, and patient depression or lethargy. As many of the nursing techniques applied to stable patients require no special equipment or advanced training (e.g., physical therapy, bladder management), clients can become adept at performing basic nursing care for dogs and cats suspected to be recumbent for long time periods. Successful nursing care of patients with neurologic dysfunction is dependent upon cooperation and communication between clinicians, nurses, and pet owners.

II. Respiratory Care¹⁻⁸

A key factor in treatment of the recumbent patient is *prevention* of respiratory dysfunction. It is of utmost importance to assess the respiratory patterns of the patient throughout the course of treatment, to auscultate frequently, and to consistently monitor oxygen saturation via pulse oximetry. Subtle changes in the respiratory system can occur within a very short time period in recumbent patients; such changes can subsequently lead to rapid deterioration of pulmonary function. Although pulse oximetry can be a useful tool in monitoring a patient's oxygenation status, it should never be substituted for a thorough physical examination. Patients must be turned every four hours or kept sternal when at all possible. Management should include sling therapy if the patient is orthopedically stable (see Physical Therapy below). Respiratory complications in the recumbent patient can be life threatening and must be addressed immediately. Stress should be minimized in the patient in respiratory distress and oxygen therapy should be administered via the most effective route. Clinicians should be aware that severe cervical lesions may compromise respiratory function. Pain may also cause changes in respiratory patterns. Thoracic radiographs should be included periodically for the recumbent patient to monitor pulmonary health. Treatments for respiratory dysfunction secondary to recumbency include oxygen therapy, nebulization and coupage therapy, positioning techniques including

sling therapy, and mechanical ventilation if respiratory complications are severe. The goals of treatment for respiratory complications include prevention of respiratory secretions and accumulation, expansion of atelectic lungs, and improved oxygenation and patient comfort.

A. Positioning techniques

Animals that are recumbent for any reason should be turned every 4 hr from left to right lateral recumbency to prevent atelectasis or accumulation of lung secretions. If atelectasis or pneumonia is present, the patient should be propped sternally or positioned with the most normal functioning lung down to improve ventilation. Postural drainage can also be accomplished by positioning the patient in a head-down posture (20° from horizontal) for 15–30 min every 4 hr to increase mucous drainage and prevent accumulation of debris within the trachea (tracheal “plugs”). It is important to supervise patients closely during treatment in order to intervene if the patient becomes stressed or if secretions obstruct the airway. Postural techniques are recommended by the authors in conjunction with nebulization and coupage therapy.

B. Nebulization and coupage therapy

Nebulization and coupage treatment for pneumonia are an effective means to move secretions from smaller airways to larger airways and to elicit coughing to remove such secretions. Acetylcysteine (Mucomyst, Bedford Laboratories) may be added to the nebulizer as a mucolytic agent. Recommended dose of 5 ml to the nebulizer for a 10% solution every 12 hr at 4–6 liters(L)/min of oxygen. It is important to practice proper technique and to minimize stress to the patient during therapy. Patients with severe pneumonia may require ventilator therapy with increased positive end-expiratory pressure (PEEP) setting to ensure expansion of collapsed alveoli.

1. Materials needed:

- handheld nebulizer (Allegiance)
- oxygen tubing
- anesthetic/oxygen machine
- 5–10 ml sterile saline
- face mask

2. Technique:

- Place the patient in sternal recumbency in a comfortable position. Sling therapy can be implemented (see Physical Therapy below) at the time of nebulization.
- Instill saline into the nebulizer compartment; do not invert the chamber.
- Connect the oxygen tubing to the oxygen system and nebulizer. Turn the oxygen to 4–5 L/min to ensure proper mist flow.

inadequate. If the patient is oxygen dependent, nasal oxygen can be utilized during therapy, if not already in use.

C. Oxygen therapy

Oxygen therapy is critical to the patient exhibiting respiratory dysfunction. Oxygen should be administered in the most effective, least stressful route. It is the opinion of the authors that nasal oxygen is far superior to oxygen cages, although oxygen cages can provide the patient immediate respiratory relief until nasal therapy can be instituted. Transtracheal oxygen can also be administered if the patient has stenotic nares or severe facial trauma.

1. Nasal oxygen tube placement

a. Materials needed:

- a soft, polyvinyl catheter ("red rubber," Kendall, Inc.)
- petroleum jelly for lubrication
- local anesthetic
- suture material
- oxygen tubing
- oxygen canister (Allegiance)
- distilled water

For facilitation of catheter placement, the patient should be restrained in a comfortable position. The gauge of the catheter should be large enough to provide adequate oxygen delivery. The authors recommend use of a size-5 French tube for a cat or small dog, and a size-8–10 French for larger dogs. Transparent feeding tubes are not recommended, as the length is excessive and the tube can be mistaken for an intravenous line.

b. Technique:

- Instill 2–3 drops of anesthetic solution into the designated nare (2% lidocaine or proparacaine).
- Lubricate the end of the red rubber catheter, and slide the catheter into the nasal cavity via the ventral meatus to the medial canthus of the opposite eye.
- The catheter should be brought up over the head either between the eyes or along the mandibular area (preferably in cats) and anchored in place beginning at the nostril by sutures.
- Oxygen tubing is connected to the catheter by either an adapter (Add-to-Adapter, Allegiance) or secured with a Chinese finger lock suture.

Oxygen tubing (the proximal end) is attached to an infusion bottle filled with distilled water. Oxygen is then delivered through the water and into the tubing connected to the catheter. If in-house oxygen is not avail-

of variable severity. The extent of tissue damage is often graded from least severe (Grade I—darkened area of thickened skin, no exposure of subcutaneous tissue) to most severe (Grade IV—deep tissue loss with exposure of bone). Grade II decubital ulcers involve exposure of subcutaneous fat, and Grade III ulcers involve tissue defects to the level of deep fascial layers.

Frequent turning of the patient and appropriate bedding represent the most important preventative measures of a nursing-care protocol. Increased skin moisture and irritation contribute to the development of decubital ulcers; therefore, patients should be kept clean and dry, and should be bathed frequently. Since decubital ulcers are primarily caused by pressure, they can be avoided or minimized by using bedding such as sheepskin, foam or air mattresses, trampolines, or bandaging techniques. Sheepskin is advantageous in that it is inexpensive and can be laundered for multiple uses. The sheepskin minimizes friction and can absorb moisture, particularly important in preventing urine scalding. Sheepskin may make patients hot, so rectal temperatures should be monitored frequently when this bedding material is used. Air mattresses are also inexpensive and allow pressure distribution to avoid decubital ulceration. Disadvantages associated with air mattresses include puncture holes from the patient's nails, and the inability to launder air mattresses for long-term use. Urine scalding can also occur with the use of air mattresses. Trampolines are excellent choice for the recumbent patient (e.g., Slee-Pee Time Beds, Inc.). The trampolines are constructed from plastic piping and fiberglass netting, allowing air to circulate underneath. The trampoline also distributes a patient's weight evenly, helping to prevent pressure sores. Urine scalding is also avoided by the fiberglass netting, as the urine falls underneath the patient onto plastic trays. Bandaging techniques in the form of doughnuts (Fig. 15.3) can also be placed over bony prominences to prevent



Fig. 15.3. Preparing a "doughnut" to place over a decubital ulcer in a dog.

decubital ulcers or over existing decubital ulcers to prevent further pressure damage. Such devices can effectively relieve pressure while allowing for adequate aeration of tissues. Treatment of decubital ulcers may involve medical and/or surgical therapies. Specific medical therapy depends upon the individual case, but may involve frequent wound lavage, systemic antibiotics, wet-to-dry bandaging, and application of topical drugs. These topical agents include antibacterial preparations (e.g., triple antibiotic, gentamicin, nitrofurazone, silver sulfadiazine ointments) and enzymatic debriding agents. Additionally, Preparation-H is believed to stimulate wound healing when applied to decubital ulcers. Surgical intervention may be required for decubital ulcers, especially if they are Grade III or IV in severity. Such intervention may include debridement and primary closure, delayed wound closure, or use of cutaneous or myocutaneous flaps.

IV. Bladder Management^{1,2,8,9,12-15}

Urinary complications are common in dogs and cats with neurologic dysfunction. Overdistension of the urinary bladder and urinary tract infections are typical sequelae, both of which are avoidable with attentive nursing care. Proper technique in both expressing and catheterizing the bladder is important to prevent urethral and bladder-wall trauma, to prevent introduction of bacteria into the urinary tract, and to measure urinary output in the oliguric or anuric patient as a guideline for appropriate fluid therapy. Poor nutrition and decreased water intake can also affect the patient's urinary system and should be corrected. Overdistension of the bladder can result in permanent atony of the detrusor muscle. The bladder should be palpated to gauge size, even if there is urine present in the cage. The presence of urine in the patient's cage is *not* a reliable indicator of the ability to urinate voluntarily; the patient could have urinary overflow as a result of distension. The bladder should be expressed every 4–6 hr as a general rule, but the urodynamics of each patient should be assessed on an individual case basis (e.g., prednisone use or IV fluids could warrant bladder evacuation more frequently). If the bladder cannot be expressed without minimal stress to the patient, a urinary catheter should be placed. Whether placing a closed urinary collection system, or intermittently catheterizing the urinary bladder, proper sterile technique must be followed in order to avoid nosocomial urinary tract infections.

A. General guidelines for urinary bladder expression

It is important to distinguish between UMN bladder and LMN bladder dysfunction to best determine which pharmacologic agents will be most efficacious in improving bladder function (see Chapter 11). Before expressing the bladder, it is advisable to first allow the patient to try to urinate voluntarily by walking or carting the animal outside. If the patient does voluntarily urinate, it is still necessary to palpate the bladder posturination to ensure complete evacuation. Catheterization may be necessary in order to gauge the amount of residual urine left after urinating if the bladder still palpates large. Normal residual urine volume in the

B



C



Fig. 15.4. Concluded.

patient is of the utmost importance. The patient should be placed in a position that will facilitate both sterile technique and successful catheterization. In the male dog, lateral recumbency is preferred, with the prepuce retracted and the penis aligned parallel with the long axis of the body (Fig. 15.5). A stylet in



Fig. 15.5. Placement of a urinary catheter in the male dog.

the catheter for the male patient is usually not required, unless urethral stones are present or suspected. When catheterizing male cats, the penis must be straightened before passing the catheter. This is accomplished by applying caudal traction to the preputial region, directing the penis in a caudal direction, parallel with the long axis of the body. Female patients can be placed either in sternal (usually preferable) or lateral recumbency (whichever is most comfortable for the patient yet optimal for the visualization of the urethral papilla). Due to the curvature and size of the papilla, a stylet in the urinary catheter is often useful when catheterizing the female patient. Mild sedation should be considered for the comfort of the patient, and to facilitate catheterization via relaxation of the urethral musculature. Urethral catheterization may be facilitated in some cases by using a syringe attachment and pulsating fluid as the catheter is being advanced.

- Position the patient for catheter placement (lateral for males, sternal for females).
- Prepare the catheter insertion site with antiseptic solution. Shave the perivulvar area in females prior to skin preparation.
- Wearing sterile gloves, inspect the balloon on the Foley catheter, lubricate the catheter, and measure the estimated length of catheter to be passed by marking the distal end of the catheter with a permanent marker.
- Pass the catheter while an assistant retracts the prepuce or vaginal folds.
- For female patients, visualization of papillae may be best accomplished with a laryngoscope light and a vaginal speculum (Fig. 15.6).
- Pass the catheter to the desired measured length.



Fig. 15.6. Visualization of the urethral papilla in the female dog, to facilitate urinary catheter placement.

For closed indwelling systems:

- Inflate the balloon of the Foley catheter with the recommended amount of saline (written on the side of the balloon arm).
- Pull the Foley catheter out of the urethra until the balloon catches on the bladder neck (females only).
- Wipe the catheter dry, and fasten it with tape and suture it in place (Fig. 15.7).
- Obtain a urine sample and attach closed system.

It is recommended to place stay sutures both around the catheter and prepuce/vulva region, with the remainder of the urinary catheter fastened around either the tail or abdominal area to prevent dislodgement. The outer portion of the urinary catheter should be labeled with permanent marker in order to monitor optimal insertion length for the duration of use. The patient should be observed closely for licking, chewing, or biting at the urinary collection system. An Elizabethan collar should be placed if a patient displays such behavior, to prevent premature catheter removal. Excessive force is contraindicated in the passage of any urinary catheter. Urethral trauma, including tears, can result from aggressive catheterization attempts; such trauma can

patient to avoid urinary flow from the bag back into the patient. If an intravenous drip set is used for the collection device, the roll clamp should be removed to avoid the mistake of restricting urine flow. The urine collection bag should be positioned at a level below the patient to ensure proper urine flow. If the patient is experiencing hematuria or urolithiasis, intermittently flushing the bladder with sterile saline is recommended. The urine collection bag should be emptied every 4 hr and urine production carefully recorded. If urine production appears inadequate, accurate placement and patency of the urinary catheter should be verified before increasing fluid administration.

In summary, to minimize urinary tract infections from an indwelling catheter, sterile technique should be observed. However, the best way to avoid urinary-tract infection is to remove the catheter as soon as it is feasible to do so. Approximately one-half of dogs catheterized for four days or longer will develop a urinary tract infection. The tip of the catheter and the patient's urine can be cultured at the time of catheter removal. If a closed urinary system is used, the prepuce or vaginal area around the urinary catheter should be swabbed every 12 hr with dilute chlorhexidine to minimize bacterial growth.

Intermittent urinary catheterization must also follow strict aseptic technique. Intermittent catheterization may be used to obtain a urine sample if a diagnosis is dependent on urinalysis and cystocentesis is contraindicated or unsuccessful. Intermittent catheterization may also be used for patients experiencing contractility difficulty; manual expression may be difficult in such patients, and may cause discomfort. It should be kept in mind that frequent intermittent catheterization may lead to patient discomfort, urethral trauma, and urinary tract infection. The practice of intermittent catheterization should only be used for the patient who does not need long-term bladder care. Finally, it is very important to keep the patient clean and housed with dry bedding in order to prevent urine scalding if the patient is recumbent and does not have a closed urinary system. As discussed previously, trampolines are available to prevent the patient from lying in urine if 24-hour care is not provided (Slee-Pee Time Beds, Inc.).

V. Physical Therapy^{1,2,9,10,12,16-19}

The major goals of physical therapy are to attain or maintain full range of joint motion, minimize muscle atrophy, and prevent or ameliorate patient discomfort. Traditional therapies of hot packing, cold packing, massage, and simple stretching exercises in veterinary medicine have been supplemented by more advanced treatments such as hydrotherapy, sling therapy, ultrasound, electrical stimulation, sling-supported exercise, and acupuncture. There is an increasing demand for prolonged post-operative care in dogs and cats, reflective of advancements in veterinary neurosurgery. Emphasis on such physical therapeutics can result in shorter hospitalization periods and improved patient well-being. A plan for physical therapy should be discussed between veterinarian, technician, and owner, in order to provide the best rehabilitation program. Benefits of physical therapy include improved circulation, increased

production of collagen, decreased inflammation, decreased muscle atrophy, and prevention of joint stiffness.

It is extremely important to have protocols of physical therapy discussed between veterinarian and technician, as patients with identical diagnoses may require different treatments. For example, animals with intervertebral disk disease may have varying degrees of neurologic impairment and will require varying degrees of physical therapy. In addition, patients recovering from vertebral fractures may receive varying stabilization techniques and will consequently receive a physical therapy regime dependent upon the surgical technique. Soft-tissue trauma, such as is often encountered in automobile accidents, may be complicated by delayed wound healing if physical therapy is instituted prematurely.

Therapeutic cold packing, or cryotherapy, is an important nursing technique for the acutely injured patient. Cold packing is efficacious in producing local vasoconstriction and in preventing interstitial bleeding, and should be the first form of therapy instituted. Owners can be instructed to apply a cold pack to the injured animal en route to the hospital. Benefits of cold therapy include reduction of enzymatic tissue activity (thereby reducing tissue destruction), and a reduction of pain perception. Typically, cold packing is performed several times a day for 20 min, up to three days after injury. Cold packs can be made by placing ice into plastic bags; alternatively, gel packs can be purchased at packing stores and kept refrigerated. It is usually best not to freeze the cold packs or plastic containers as the packs become difficult to mold around the injured area. Subzero blankets, which circulate cold water, can also be purchased at hospital pharmacies and can be useful in cold-packing procedures. In addition, subzero blankets can be utilized for head-trauma patients by decreasing total body temperature in order to decrease intracranial pressure (see Chapter 5). Hot packing should follow cold therapy after 72 hr. *Therapeutic hot packing* in the form of moist, heated towels is a common form of physical therapy used to relieve pain, decrease tissue edema resulting from inflammation, relax muscle spasms, and increase circulation. Hot packing prior to stretching exercises can also promote flexibility and increase range of motion. Moist heat is recommended for hot-packing therapy, such as warm moistened towels or hot water bottles. Heat therapy should be implemented after 72 hr and applied every 6–8 hr for 20 min around the affected area. It is not recommended by the authors to use heating pads for heat therapy, particularly for animals recovering from anesthesia, or patients with sensory nerve impairment. Use of such devices may lead to thermal burns.

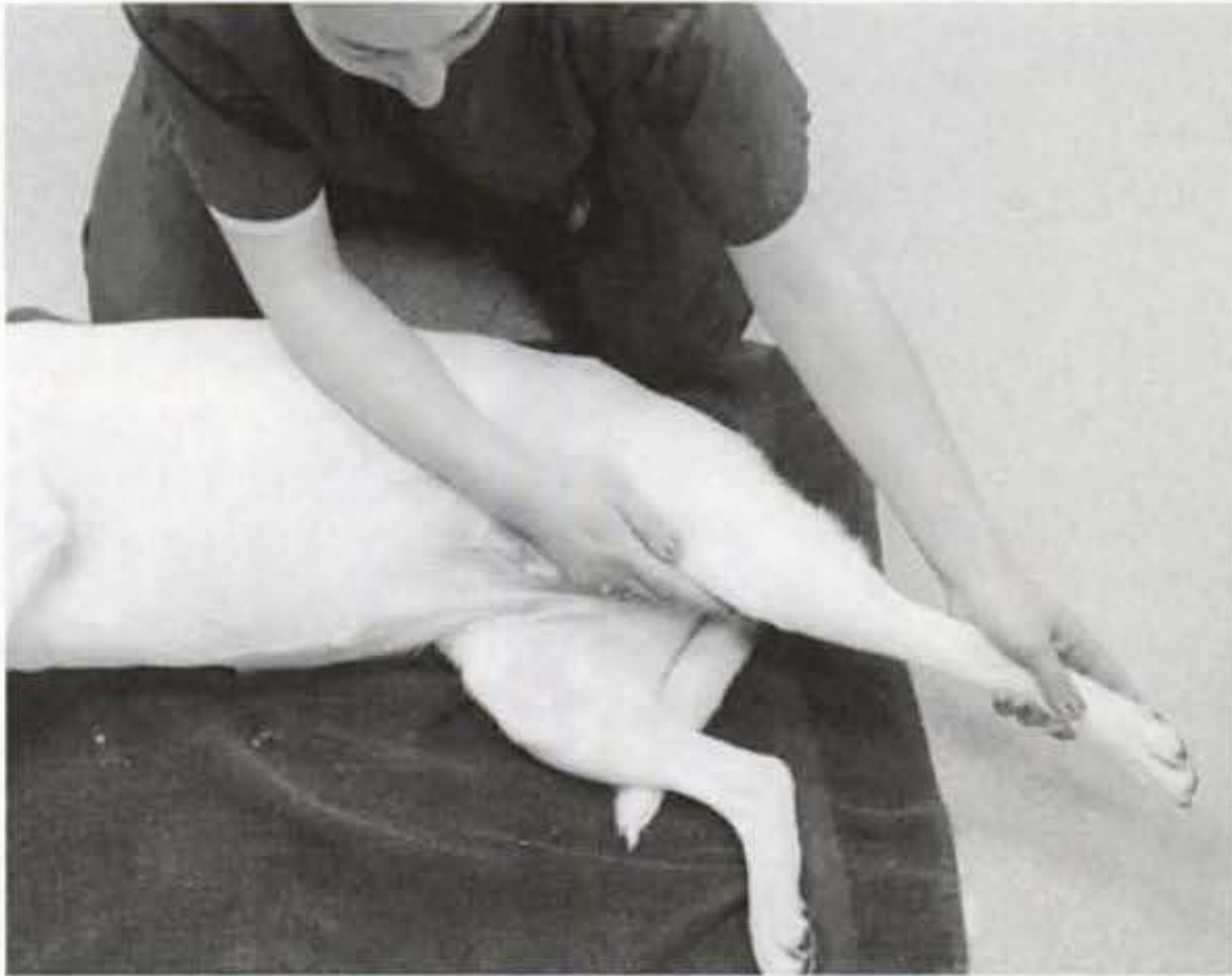
Massage is another form of physical therapy used in veterinary medicine. Manipulation of the tissue by simple hand technique can increase circulation, loosen stiff muscles, reduce excess interstitial fluid, and minimize muscle atrophy. Massage can also be beneficial prior to stretching exercises to improve range of motion, relax the patient before more aggressive therapy can be instituted, and provide increased circulation. Techniques such as compression, kneading, and stroking (effleurage) are effective therapies, particularly in the recumbent patient. Goals of massage must be communicated between veterinarian and technician, and appropriate rhythm, pressure, duration, and frequency established on an individual basis. *Effleurage* is by definition a deep-stroking movement specifically designed to circulate venous blood flow

and encourage lymphatic drainage. Typically, massage begins with effleurage in order for the technician to assess the patient's pain response, muscle tone, and detection of any fibrotic areas. The pressure of massage may vary, depending on the goal of massage therapy. Appropriate pressure should be light to moderate in order to relieve tension and to decrease edema. If fibrotic areas are present, pressure of massage should be increased. It is important to monitor response in the patient and to avoid excessive pain. Massage therapy should be implemented three to four times daily, for 10–15 min to each affected area, in conjunction with other forms of therapy mentioned below. Technique of massage or effleurage may vary. The authors prefer to start with the distal aspect of each affected limb, and apply light to moderate pressure in smooth movements with the fingertips running lateral and medial before returning distally and removing pressure. Kneading or twisting the skin may also improve circulation and create an effective massage to larger muscular groups, using the palm of the hand. Massage technique should not be applied to areas with soft-tissue damage or skin grafts.

Stretching, or *passive range of motion* exercises are an important form of physical therapy that can be performed by both technician and owner. Benefits of passive range of motion include joint homeostasis, preventing range of motion loss in joints, improved circulation and lymphatic drainage, prevention of muscle atrophy, and prevention of tissue adhesions. Similar to other forms of physical therapy, it is important for effective communication between veterinarian and technician with regard to the goals of physical therapy on an individual basis. Ideally, passive range of motion exercises should begin the day after surgery or injury, unless there is severe soft-tissue damage or orthopedic injury. Passive range of motion is accomplished through a series of repetitious motions. It is the authors' opinion that each limb should be cycled individually in order for adequate assessment of function and range of motion of all limbs. By holding the foot with one hand and grasping the caudal aspect of the stifle or elbow with the other, the limb is pulled forward and then back in a cycling motion (Fig. 15.8). It is recommended to perform 5–10 flexions and extensions first on individual joints before flexing the entire limb. Flexion and extension exercises should be scheduled at least three times a day. Particular attention should be given to the limb that is injured or surgically repaired and caution used with regard to the patient's pain response. Geriatric patients require careful flexion, as fragility of bone density may be an issue. Patients with sensory nerve impairment must also be flexed with caution, as pain response may be absent. The goal of passive range of motion is to cycle the limbs through a normal range of motion with normal joint motility. Hot packing and massage may be initiated prior to range of motion exercises to facilitate muscle and joint compliance. Combining sling therapy with passive range of motion exercises can also provide added physical benefit to the patient. Providing a more natural sternal position without added limb stress permits gravity to pull the limbs for increased circulation and stimulation. The gravity supplied by the sling will also promote drainage and decrease edema that often develops with recumbent patients.

Sling therapy is an important aspect of physical therapy, particularly in the recumbent patient. Slings can be constructed out of plastic piping (Fig. 15.9) or aluminum welded pipes (Fig. 15.10) for long-term use. Sliding pipes can hold canvas or cloth

A



B



Fig. 15.8. Passive range of motion exercises, extension (A) and flexion (B).

harnesses with holes to place each limb. Either design can provide the patient with adequate support to maintain sternal positioning for therapy exercises or chest physiotherapy. Limb edema is decreased with the use of sling therapy, and provides optimum positioning for massage, range of motion exercises, and nebulization/coupage therapy. Bladder care can be easily addressed while in the sling using manual tech-



Fig. 15.9. Support sling constructed of plastic piping material.

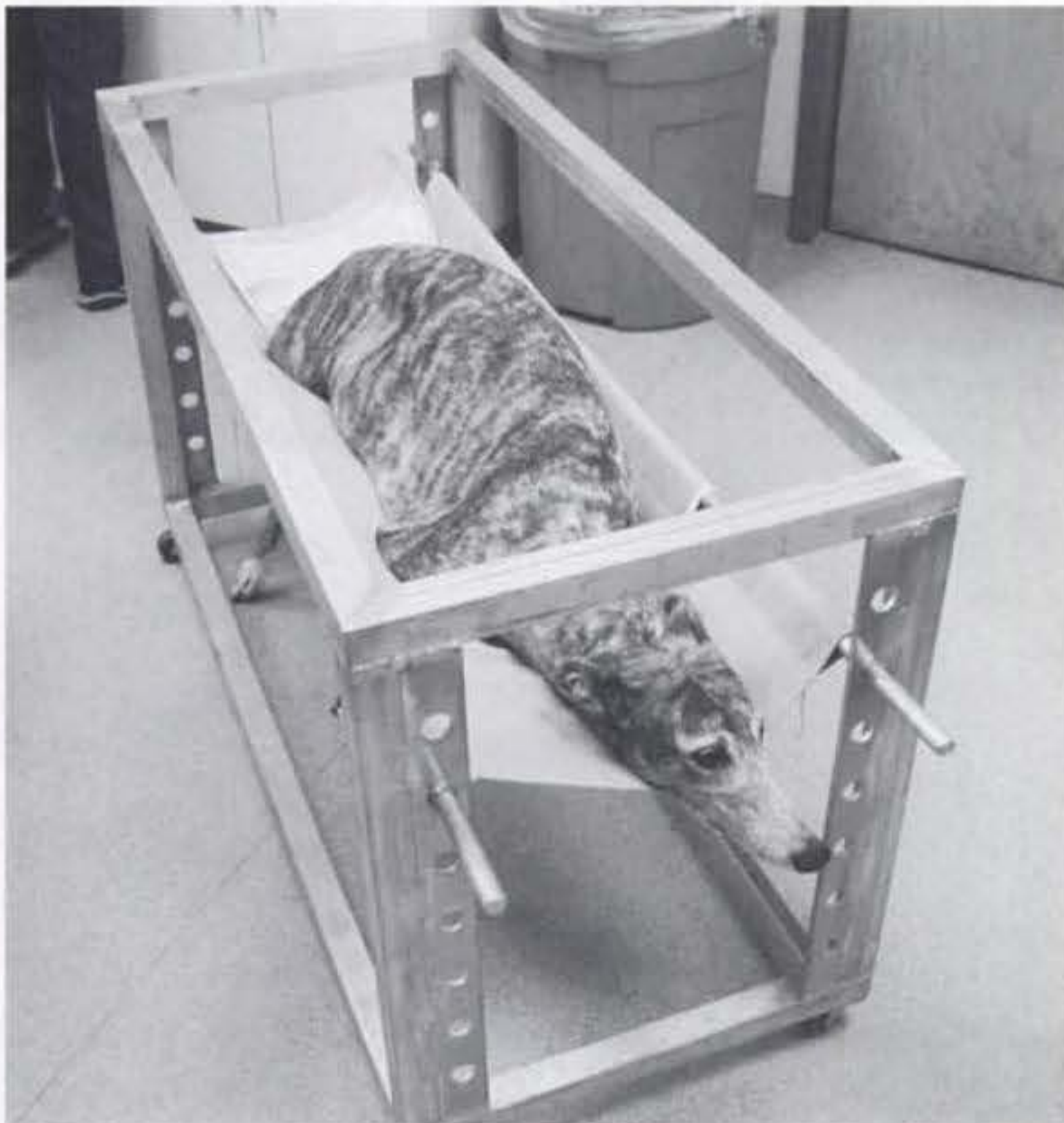


Fig. 15.10. Support sling constructed of aluminum welded pipes.

niques; the patient can also be encouraged to urinate voluntarily while in an upright position. In addition, placing a patient in a sling provides sternal positioning for feeding, which is important in the recumbent patient to prevent aspiration pneumonia. Patients placed in slings should have the pads of the feet touching the floor mats,

to encourage voluntary motion. Slings with wheels attached can allow patients to walk about the hospital with little aid or support. Owners can be encouraged to build a sling apparatus device for long-term paresis/paralysis patients. Sling therapy is particularly useful in preventing lung atelectasis and accumulation of respiratory secretions in dependant airways. Lung consolidation can occur with any patient that is recumbent (see respiratory therapy above). The sling provides the patient a means to stay sternally recumbent; this enhances drainage of respiratory secretions, lung expansion, and overall ventilatory efficiency. Caution should be exercised when placing the patient into the sling as the patient may have stiff joints or various orthopedic conditions. Recumbent patients should be placed in a sling every 4–6 hr, with physical therapy sessions in conjunction with sling therapy, chest physiotherapy, hot or cold packing, bladder care, and feeding. Patients should remain in the sling for 30 min to an hour, and be monitored closely for discomfort or anxiety. The patient may require additional cervical or thoracic support in the form of pillows or rolled towels while in the sling. Initially, it may be necessary to place a patient in the sling device for shorter periods until the patient has adjusted to being constrained in an upright fashion. During sling therapy, the patient should be monitored closely, particularly if the patient has pneumonia (see respiratory therapy above). Respiratory patterns should be monitored to ensure that the animal is not stressed during therapy.

Hydrotherapy is another form of physical therapy advantageous to the neurologically impaired or recumbent patient. Hydrotherapy, or swimming exercise, provides extensive joint and muscle activity in a non-weight-bearing setting. Hydrotherapy can be achieved using a tub or pool equipped with an electric pump to create waves or ripples against which patients swim (Fig. 15.11). Patients need close supervision



Fig. 15.11. Hydrotherapy of a paretic patient, using a treadmill apparatus (Courtesy of Allan Dahl, the Ferno company).

during hydrotherapy to prevent drowning or severe injury. Flotation devices designed specifically for canine use are recommended during hydrotherapy. Physical support to the cervical and thoracic areas is recommended during hydrotherapy, even with flotation device use. If the patient becomes overly distraught or frantic during hydrotherapy, treatment should be discontinued and attempted again the next day. Hydrotherapy should be limited to 5 min per day, as swimming exercises are very exhausting.

Exercise for the recumbent or neurologically compromised patient can be accomplished by use of body slings or towels. Towel walking a patient can be a safe way to begin exercises and to encourage muscle movement (Fig. 15.12). It is important to support the paretic area with a towel and to prevent the limbs from dragging on the ground. Tail walking, or using the tail as a means to hold a patient in upright fashion, is generally not recommended. Towel walking should not be practiced in patients with unstable vertebral fracture/luxations, or patients with orthopedic problems that may be exacerbated by towel walking (e.g., pelvic fractures). Paraparetic patients can also be exercised by means of *body slings* (Walkabout Harnesses, Santa Cruz). These slings maximize patient comfort, provide superior support, and are convenient for pet owners (Fig. 15.13). The paretic limbs should not be dragged along the ground while the sling is used; rather, the harness should elevate the patient so that the limbs are supported slightly by the ground surface. This will encourage voluntary movement and prevent abrasion of the toes. Pet owners should be encouraged to purchase the body slings and assist their pets in early postsurgical ambulation.



Fig. 15.12. Towel walking a paraparetic dog.

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Chapter 16

PHARMACOLOGIC MANAGEMENT OF PAIN

Curtis W. Dewey

I. Introduction¹⁻¹⁹

That dogs and cats with certain neurologic disorders experience pain is without question. Various behavioral (e.g., vocalizing, inappetance, lethargy) and physiologic (e.g., mydriasis, hypertension, tachycardia) parameters are useful indicators of animal suffering. However, such parameters are not consistent enough among dogs and cats (especially) for reliable assessment of the presence and degree of patient discomfort. Clinicians are often reticent to administer analgesic drugs to patients, primarily due to persisting misconceptions regarding animal pain control. Concern over potential adverse drug effects, especially with opiates, often leads to avoidance of analgesic administration. While the possibility of adverse drug effects should not be ignored, the clinician should bear in mind that such effects are extremely rare, especially in the awake, painful patient. Adhering to maximum dose recommendations of analgesic drugs will also help minimize adverse effects. Conversely, there is abundant evidence that untreated pain is associated with increased patient morbidity. Dogs and cats whose pain is unaddressed are at increased risk for immunosuppression, inappetance/anorexia (of particular concern in cats, as they are prone to developing hepatic lipidosis), gastrointestinal disturbances, hypertension, and cardiac arrhythmias (e.g., atrial and ventricular premature contractions). This chapter provides an overview of the pathophysiology and anatomy of pain perception in dogs and cats, and focuses on the common analgesic drugs used to control pain in these species. Attentive nursing care and physical therapy are of vital importance in maintaining patient comfort; these subjects are covered in Chapter 15. Acupuncture is becoming increasingly recognized as an effective means of pain control, and is discussed in Chapter 17.

II. Pathophysiology and Anatomy of Pain Perception^{8-10,17,18,20-22}

Nociceptors are specialized dendritic zones of neurons whose cell bodies are located in the dorsal root ganglia. These sensory receptors are located throughout the body and serve to transmit noxious stimuli from the periphery to the central nervous system (CNS). Nociceptors can be directly or indirectly (i.e., lowered threshold for depolarization) activated by a number of inflammatory mediators, including prostaglandins, leukotrienes, histamine, bradykinin, and substance P. The axons of nociceptors are small-diameter, myelinated (A-delta), and nonmyelinated (C) fibers. A-delta fibers conduct action potentials at a rate of 5–30 meters/second (m/s), and convey sharp, acute pain. C fibers conduct at a rate of less than 1 m/s, and are responsible for dull, throbbing pain conveyance. Distal axons of nociceptors enter the

dorsal gray column of the spinal cord; the tract formed by the convergence of these axons at the dorsolateral aspect of the spinal cord is aptly named the dorsolateral fasciculus. These axons synapse on *nociceptive neurons* in various laminae of the dorsal gray column. The major neurotransmitter released by the distal axonal terminals of both A-delta and C fibers is glutamate. This excitatory neurotransmitter targets N-methyl-D-aspartate (NMDA)-type glutamate receptors on dorsal horn nociceptive neurons, with resultant neuronal depolarization. In addition to glutamate, substance P is released at the axonal terminals of C fibers. Nociceptive neurons of the dorsal gray column convey impulses to the brain via several spinal tracts; these include the spinothalamic tract, spinocervicothalamic (cervicothalamic, spinocervical) tract, spinoreticular tract, and fasciculus proprius. For the majority of these pathways, numerous ipsilateral and contralateral synapses occur as action potentials are propagated cranially through the spinal cord toward the ventrocaudolateral nucleus of the thalamus (VCLNT). Therefore, spinal transmission of painful stimuli is a multisynaptic system, involving both sides of the spinal cord. Activated neurons of the VCLNT project their axons via the internal capsule to the ipsilateral somesthetic cerebral cortex for conscious perception of pain.

Several regions of the brain stem contain neurons whose axons descend the spinal cord, inhibiting nociceptive neurons of the dorsal horn. One such pathway involves the periaqueductal gray matter of the midbrain and the median raphe nuclei of the medulla. Neurons of the periaqueductal gray matter of the midbrain synapse with serotonergic neurons of the medullary raphe nuclei. These latter neurons project their axons caudally to inhibit nociceptive dorsal horn neurons in the spinal cord. Other, similar pain-inhibiting systems are located in various regions of the medulla and pons, including the locus ceruleus of the pons.

With repeated application of a painful stimulus, a phenomenon called *sensitization* may occur in both the periphery and the CNS. In a given region of nociceptors where the initial stimulus occurs, continued production of inflammatory mediators (e.g., prostaglandins, leukotrienes) will lead to recruitment of additional nociceptors in the nearby vicinity of the original stimulus site. In the CNS, repetitive or prolonged activation of NMDA-type glutamate receptors of dorsal horn nociceptive neurons may eventually lead to these neurons becoming hyperexcitable to further input from nociceptive afferents. Sensitization results in a situation in which a painful stimulus produces a more intense feeling of pain than would have occurred with the same stimulus prior to sensitization. Sensitization represents a physiologic reason for early analgesic intervention in the painful patient.

III. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)^{11,12,14-19,23-28}

Numerous inflammatory mediators are produced via the actions of cyclooxygenase (COX) and lipoxygenase enzymes on arachidonic acid. Arachidonic acid is a fatty acid released by the action of phospholipase A₂ on damaged cellular membranes. Prostanoids (prostaglandins, thromboxane) are produced via the COX pathway, for which there are two important enzyme isoforms (COX-1 and COX-2). Leukotrienes are products of the lipoxygenase pathway. Prostanoids and leukotrienes are impor-

tant mediators of inflammation and pain, both peripherally and centrally. Prostaglandin E₂ (PGE₂) also sensitizes nociceptors to bradykinin and histamine. The majority of the prostanoids formed by the COX-1 pathway are involved in normal homeostatic mechanisms. Prostaglandin E₁ is important for normal gastrointestinal function as it promotes bicarbonate and mucus secretion, helps maintain normal mucosal blood flow, and decreases production of hydrochloric acid. Prostacyclin (PGI₂), a prostaglandin with vasodilatory actions, functions in part to maintain normal blood flow to the kidneys. Thromboxane A₂ promotes platelet aggregation, and is necessary for normal blood clotting. The COX-2 pathway is responsible for producing most of the prostanoid inflammatory mediators. This enzyme pathway is induced by tissue damage and inflammation. In the face of tissue injury, COX-1 activity typically increases two to three times over baseline, whereas COX-2 activity increases twentyfold over baseline levels.

Dose recommendations for nonsteroidal anti-inflammatory drugs (NSAIDs) commonly used in dogs and cats are provided in Table 16.1. These drugs act primarily via inhibition of COX enzyme pathways. In contrast to aspirin, some of the newer NSAIDs (e.g., carprofen, etodolac) are preferential COX-2 inhibitors, with little effect on COX-1 function. There is also some evidence that certain NSAID drugs (e.g., ketoprofen) may inhibit the lipoxygenase pathway to some degree. Although traditionally thought of as acting in the periphery, some NSAIDs may also provide analgesia by inhibiting COX enzyme activity in the CNS. Other suspected analgesic actions of NSAIDs in the CNS include inhibition of NMDA-type glutamate receptors, blocking serotonin release, and modulation of endogenous opioids. Inhibition of substance P release and bradykinin may also be important analgesic functions of some NSAID drugs.

Nonsteroidal anti-inflammatory drugs are typically used for mild to moderate pain. However, ketoprofen has been shown to be similar in apparent analgesic effect to buprenorphine and meperidine in cats. The potential side effects of NSAIDs are primarily related to their effects on the COX-1 enzyme pathway. These side effects include gastrointestinal irritation, renal damage, and increased tendency to bleed. Although use of COX-2 preferential NSAIDs substantially decreases the chances of such adverse drug effects, the clinician should be aware that severe hepatotoxicosis has been reported with carprofen use in dogs. Since cats are deficient in hepatic conjugative pathways necessary for NSAID metabolism, strict adherence to dosing recommendations for this species is mandatory. In general, NSAID use should be

Table 16.1: Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Commonly Used for Analgesia in Dogs and Cats

Drug	Canine dosage	Feline dosage
Aspirin	10–25 mg/kg PO, q 8–12 hr	10 mg/kg PO, q 72 hr
Ketoprofen	1–2 mg/kg IV, IM, SQ, PO, q 24 hr	0.5–1.0 mg/kg IV, IM, SQ, q 24 hr, up to 3 days; PO up to 5 days
Carprofen	2 mg/kg PO, q 12 hr	Not recommended
Etodolac	10–15 mg/kg PO, q 24 hr	Not recommended

Table 16.2: Opioid Analgesic Drugs Commonly Used in Dogs and Cats

Drug	Canine dosage	Feline dosage
Morphine	0.05–1.0 mg/kg slow IV, IM, SQ, q 4 hr CRI: 0.1–0.5 mg/kg/hr IV	0.05–0.1 mg/kg IM, SQ, slow IV, q 4 hr CRI: 0.05–0.1 mg/kg/hr IV
Fentanyl	0.002–0.005 mg/kg IV, IM, SQ, q 1–2 hr CRI: 0.003–0.006 mg/kg/h IV Fentanyl patch: <5–10 kg–25 µg/h <10–20 kg–50 µg/h <20–30 kg–75 µg/h >30 kg/100 µg/h	0.001–0.003 mg/kg IV, IM, SQ, q 2–4hr CRI: 0.002–0.003 mg/kg/hr IV Fentanyl patch: 25 µg/hr
Oxymorphone	0.05–0.1 mg/kg IV, IM, SQ, q 4–6 hr	0.02–0.05 mg/kg IV, IM, SQ, q 4–6 hr
Hydromorphone	0.05–0.2 mg/kg IV, IM, SQ, q 4–6 hr	0.03–0.1 mg/kg IV, IM, SQ, q 4–6 hr CRI: 0.02 mg/kg/hr IV
Butorphanol	0.2–0.4 mg/kg IV, IM, SQ, q 2–4 hr 0.5–2.0 mg/kg PO, q 6–8 hr	0.2–0.4 mg/kg IV, IM, SQ, q 2–4 hr 0.4–1.0 mg/kg PO, q 8 hr
Buprenorphine	0.01–0.02 mg/kg IV, IM, SQ, q 6–8 hr	0.005–0.01 mg/kg IV, IM, SQ, q 6–8 hr
Codeine (Tylenol #4)	1–2 mg/kg (of codeine) PO, q 8–12 hr	Strictly contraindicated

release. Vomiting is another predictable untoward effect of IV morphine bolusing. Cats may be more sensitive to these effects of IV morphine bolus delivery, and the intramuscular (IM) or subcutaneous (SQ) routes of administration are often preferentially recommended for this species. However, if the morphine bolus is diluted with saline and administered slowly over several minutes, hypotension and nausea/vomiting are unlikely to occur in either cats or dogs. Cats appear to be less able to convert morphine to active metabolites, in comparison with dogs. Also, the onset of action for morphine is prolonged in cats, compared with dogs. Morphine is more commonly used as a continuous rate infusion (CRI), rather than repeated bolus infusion. An initial morphine bolus or “loading dose” of morphine is often given, followed by institution of the CRI.

Fentanyl is approximately one hundred times more potent than morphine; its short duration of action necessitates either frequent IV administration or (preferably) CRI. Fentanyl may be the safest narcotic for use in cases with increased intracranial pressure (e.g., head trauma). As with morphine, an initial “loading dose” of IV fentanyl is often administered immediately preceding institution of a fentanyl CRI. The duration of analgesia afforded by a fentanyl CRI is the length of time the drug is

infused plus an additional 30 min following discontinuation of the CRI. The transdermal fentanyl delivery system, or fentanyl patch, is a very convenient, safe, and reliable method of fentanyl administration in dogs and cats. There are four different patch "sizes" (rates of fentanyl release) for different body-weight categories. Because of the continuous transdermal delivery method, peaks and troughs of serum fentanyl levels are not likely, compared with intravenous administration. It appears to take 3–6 hr in cats, and 12–24 hr in dogs, for adequate serum fentanyl levels to be attained following patch application. An alternative mode of analgesia may be necessary during this time period. A region of the dorsal cervical skin should be shaved for fentanyl patch application. The site should not be scrubbed with soap or alcohol. It is advisable to hold the patch by the edges and wear gloves during application. The duration of effective analgesia provided by the fentanyl patch is approximately 3 days. There is evidence that this period is longer (more than 4 days) in cats. In dogs, it takes between 2 and 12 hr for serum fentanyl to reach subtherapeutic levels following patch removal. The rate of fentanyl release increases with increasing temperature. Heating pads must be kept away from the fentanyl patch, and the patch should be used with caution in febrile patients. Fentanyl patches are not recommended for patients weighing less than 3.5 kg. Fentanyl patches are recommended for use in hospitalized patients, in order to prevent any owner misuse of the patch. If a patient is sent home with a fentanyl patch, arrangements should be made for the veterinarian to discard the patch once it has expired.

Oxymorphone and hydromorphone are similar opioid drugs that have minimal side effects, and duration of analgesia up to 6 hr. Oxymorphone is approximately ten times more potent than morphine, and hydromorphone is roughly five to seven times more potent than morphine. The author prefers to use these drugs in the immediate postoperative period (i.e., first 24 hr), giving one-half of the dose IV, the other half IM or SQ. The main advantage of hydromorphone over oxymorphone is cost; hydromorphone is approximately eight times less expensive than oxymorphone. Hydromorphone is a very safe and effective analgesic drug choice for feline patients, especially when used as a CRI.

Butorphanol and buprenorphine are mixed agonist/antagonist opioid drugs, primarily used to treat patients with mild to moderate pain. Butorphanol appears to exert its analgesic effects primarily by acting at κ receptors. Butorphanol is a μ antagonist. Buprenorphine is a partial μ agonist, and a κ antagonist. These drugs are very safe, cause minimal sedation, and provide up to 6 hr (buprenorphine may provide up to 8 hr) of analgesia. Buprenorphine is generally considered to be a more effective analgesic agent than butorphanol. Both butorphanol and buprenorphine exhibit a "ceiling effect" on respiratory depression, such that increasing the dose of the drug will not lead to exacerbation of respiratory depression. Unfortunately, these drugs also seem to exhibit a "ceiling effect" in reference to their analgesic actions; this is probably due to the fact that they have antagonistic as well as agonistic actions on opiate receptors. Because of the mixed agonistic/antagonistic nature of these drugs, it is not wise to mix them with pure opioid agonists.

There are limited options for oral administration of opioid drugs to dogs and cats. Butorphanol can be a useful oral analgesic for both cats and dogs, but may be

prohibitively expensive in the latter species. Oral codeine can be given to dogs in an acetaminophen/codeine combination. This drug should *never* be given to cats, and should be avoided in dogs with hepatic disease.

In the unlikely event of a narcotic overdose, a narcotic antagonist can be administered. Naloxone, a pure opioid antagonist, is primarily active at μ receptors, with some κ receptor antagonism. The objective of naloxone administration is to reverse adverse effects of a narcotic (e.g., respiratory depression, excess sedation), without obliterating the analgesic effect of the narcotic. This is achieved by diluting the drug with normal saline, and delivering it slowly and to effect. The dose of naloxone is 0.04 mg/kg body weight. The desired amount should be diluted approximately 1:100 (e.g., 0.1 ml of a 0.4 mg/ml naloxone solution diluted with 10 ml of normal saline) and administered slowly IV (approximately 1.0 ml/min) until the adverse narcotic effects are reversed.

V. Sedative/Tranquilizer Drugs^{10,12-14,17,19,28}

Pain can be exacerbated in the extremely stressed or anxious patient. Although sedative/tranquilizer drugs do not provide analgesic effects, they may be useful in such patients when used in combination with analgesic drugs.

Acepromazine is a very effective sedative/tranquilizer drug, but can lead to severe hypotension. Hypotension is particularly more likely to occur in elderly or debilitated patients. The author recommends a conservative dose of 0.01 mg/kg body weight (1/2 IV, 1/2 SQ or IM). If this initial dose is ineffective, additional 0.01 mg/kg doses are administered, up to a maximum dose of 0.05 mg/kg body weight. Acepromazine has a long duration of action and may have effects for 6–12 hr. There is concern that acepromazine may lower the seizure threshold, and is therefore relatively contraindicated for use in dogs and cats with seizure disorders or other encephalopathies. Despite this concern, a causal link between acepromazine administration and increased seizure frequency is poorly substantiated in the veterinary literature. In the author's experience, short-term administration of low-dose acepromazine to patients with encephalopathies does not appear to increase seizure frequency in these animals.

The benzodiazepines, diazepam and midazolam, are very safe and effective sedative/tranquilizer drugs. The recommended dose for these drugs is 0.2 mg/kg body weight IV. The main disadvantage of these drugs is the short duration of action, especially in dogs, and particularly for midazolam.

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Chapter 17

COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR PATIENTS WITH NEUROLOGIC DISEASE

Karen L. Kline

I. Introduction

Neurologic disease in the canine and feline veterinary patient can affect multiple locations, including the brain, spinal cord, and neuromuscular system. A multitude of clinical signs is possible, ranging from behavior changes to seizures, and weakness to paralysis. Pain, or hyperesthesia, is often the principal or sole clinical sign of neurologic disease. The incorporation of complementary and alternative medicine into conventional medical practice in the human arena has piqued interest on the subject in veterinary medicine. Complementary and alternative veterinary medicine (CAVM) encompasses a broad spectrum of treatment modalities, including acupuncture, chiropractic, herbology, light therapy, and massage therapy. Other therapies exist and are used alone or in combination with the above treatments. The goals of incorporating CAVM into conventional practice are to (1) improve the quality of life of the patient and owner, (2) diminish pain, and (3) incorporate a more holistic view of the veterinary patient. The use of CAVM in the treatment of neurologic disease has the same goals as previously mentioned. The use of CAVM for neurologic disease includes selective and adjunctive treatment of seizures, cerebrovascular disease, vestibular disease, intervertebral disk disease, myopathies, and neuropathies. CAVM may be particularly helpful to those patients who (1) have nonsurgical lesions, (2) are geriatric, or (3) are anesthetic risks. The key point to remember is that CAVM can be used in combination with conventional medicine once a definitive diagnosis has been established and all options are offered to the owner. The goal of this chapter is to (1) familiarize the reader with CAVM and its use in the treatment of various neurologic diseases that affect companion animals and (2) provide scientific evidence for its validity and efficacy.

II. Acupuncture¹⁻³⁰

Acupuncture has been used for thousands of years and has its roots in Chinese and ancient Indian cultures. It was first introduced into Western civilization in the early 1900s and has since gained popularity as a mode of therapy for multiple diseases. Acupuncture revolves around the Eastern theory of Yin, Yang, and Qi. The theory behind acupuncture involves the stimulation of specific anatomic points in the body to achieve a therapeutic effect. This scientific theory of acupuncture centers around the acupoint, of which there are an estimated 365 on the body surface. An acupoint can vary in size from 2 mm to 50 mm, and is composed of a triad of connective tissue, a nerve bundle, and a vascular bundle; triads have been visualized via electron

microscopy. Acupoints are joined by theorized meridians or pathways; there are 14 major meridians that run on the body surface and connect the acupoints, which have a very low electrical resistance. Stimulation of acupoints has been shown to stimulate release of inflammatory mediators such as corticosteroids, endorphins, and enkephalins. The scientific basis of acupuncture is being studied through multiple NIH grants and there are a number of theories surrounding its efficacy. Several processes have been proposed to explain acupuncture's effects, focusing mainly on pain. When acupuncture points are stimulated, the central nervous system is thought to release chemicals such as hormones into the muscle, spinal cord, and brain that may help to modulate the experience of pain and to promote the body's natural healing abilities.

Three main mechanisms are proposed to explain the clinical effects of acupuncture: (1) conduction of electromagnetic signals in which stimulated acupoints are thought to be conductors of such signals at an increased rate; such signals promote the flow of biochemicals such as endorphins and enkephalins, as well as stimulating immune system cells; (2) activation of opioid systems, in which several types of opioids may be released centrally during treatment, thus decreasing pain; and (3) changes in brain chemistry, sensation, and involuntary body functions by altering the release of neurotransmitters and neurohormones in a positive manner. One theory, the "Gate Theory," is explained in more detail below under the heading of Physical Therapy. Acupuncture therapy can be administered using needles alone (Fig. 17.1), needles and electrical stimulation, acupressure, aquapuncture (injection of Vitamin B₁₂ or saline into acupuncture points), and low-intensity light therapy (cold laser therapy). Each modality of therapy is tailored to the individual patient's signs, symptoms, and temperament. Treatments can be administered on a daily, weekly, or monthly basis, depending upon the underlying problem and goals of therapy. Neurologic conditions amenable to acupuncture therapy include brain disorders such as epilepsy, head trauma, cerebrovascular events; spinal cord disorders such as nonsurgical intervertebral disk disease (mostly Type 2) of the cervical, thoracolumbar, or lumbosacral regions; and neuromuscular disorders such as masticatory myositis, idiopathic facial nerve paralysis, and trigeminal neuritis.

III. Chiropractic^{15,16,21,30,31}

Chiropractic manipulation has been a mode of therapy in human medicine for a number of years and, like acupuncture, has become very popular in the treatment of companion animals. Chiropractic theory is based upon manual spinal manipulations and revolves around the relationship and interactions between spine biomechanics, and neurologic mechanisms. Therapy is aimed at the vertebral column to alter disease progression. Multiple terminologies are used in chiropractic care. The term "subluxation" is commonly used and implies an abnormal positional relationship of the vertebral bodies that can have an effect upon normal biomechanical and neurologic function. The pathophysiology of subluxations is associated with numerous theories, including the facilitation hypothesis, which states that subluxations produce a low-

of nociceptive transmissions, with the goal of improving joint function and pain alleviation. In veterinary medicine, similar concepts apply, with multiple applications that range from active movement of the joints between vertebral segments to those using low-force techniques. Multiple techniques and treatment theories (ranging from the role of CSF in spinal column function to potential neuropathology at the intervertebral foramen) make this treatment modality controversial in veterinary medicine. The goal of the veterinary chiropractor is to divide the spinal column into functional sections or "motor units" for a more concise concept of the biomechanics of spinal movements, malalignments, and adjustments of subluxated segments. A motor unit is comprised of two adjacent vertebrae, as well as the intervertebral disk, articular facets, ligaments, muscles, tendons, nerves, and blood vessels that unite the two vertebrae as one unit. It should be noted that the term "motor unit," as used in the realm of chiropractic medicine, has a completely different meaning than the same term used to describe the neuroanatomy of muscle innervation (see Chapter 13). The chiropractic philosophy is based upon the concepts of homeostasis; this therapy, like acupuncture and other alternative therapies, must be tailored to the individual patient and performed when an adequate diagnosis has been made and all options are discussed with the client.

Indications for chiropractic therapy in the neurologic small-animal patient can include (1) spinal hyperpathia (cervical, thoracolumbar, lumbar) in the absence of progressive neurologic deficits in cases of intervertebral disk disease; (2) neuromuscular disease; (3) muscle ligament, bone, or tendon pain most commonly associated with underlying orthopedic disease that is either chronic or acute (i.e., traumatic); or (4) degenerative disease (spondylosis associated with the vertebral column). However, the role of veterinary chiropractic has not been fully researched in veterinary medicine and questions still exist regarding its indications for use and its true efficacy. It is not, however, a replacement for conventional therapy if the patient is exhibiting a deteriorating spinal cord condition, such as neoplasia, or intervertebral disk rupture with resultant acute paralysis.

IV. Massage Therapy^{15,16,21,30}

Massage therapy in veterinary medicine has increased in popularity within the last ten years. It is especially popular in the equine sector, but is also used quite extensively as a subcategory of physical therapy in small-animal medicine and surgery. It is defined as the intentional and systematic manipulation of the soft tissues of the body to enhance health and healing. The primary characteristics of massage are the applications of touch and movement. The scientific rationale behind this therapy implies that the function of the hands and the mechanical pressure exerted on cutaneous and subcutaneous structures affect the body. Enhancement of blood and lymph circulation is achieved resulting in increased oxygen supply and, in theory, the removal of endogenous waste products. It is theorized that direct mechanical pressure and the effects mediated by the nervous system can benefit areas of increased muscle tension. It is also theorized that massage stimulates the parasympathetic nervous system. That

can result in relaxation and pain reduction through two different neural-gating mechanism theories. One, as mentioned previously in the effects of acupuncture, is the "Gate Theory" of pain control. This theory suggests that a gate or gates exist throughout the spinal cord. Peripheral pain messages travel to these spinal cord gates and, depending on whether or not these gates are open or closed, the pain message travels on to the brain where it is recognized. Involved in this theory are two types of nerves: the A-delta, small-diameter fibers that originate from nociceptive (pain) receptors, and the A-beta, large-diameter fibers that are sensitive to touch, pressure, and warmth. Both are theorized to stimulate T cells in the spinal cord and then send messages to the brain. T-cell activity is also mediated through the substantia gelatinosa (SG), which is also associated with the spinal cord and receives input from the A-beta fibers. When the SG is stimulated, the T-cell activity closes "the gate." Opposing this, the delta fibers sensitive to pain interfere with this SG activity, thus the T-cell activity is increased and "the gate" opens, allowing pain impulses to be recognized by the brain. The "Gate Theory" implies that massage therapy closes "the gate" (stimulates the A-beta fibers) and thus decreases the patient's pain perception. The second theory states that massage increases restorative sleep, resulting in the decreased release of substance P, a pain neurotransmitter. Relaxation through massage is thought to decrease oxygen consumption and metabolic rate, reduce blood lactate, decrease blood pressure, decrease muscle tension, and increase blood flow, although reports in the human literature have been mixed.

Massage therapy in veterinary medicine is best used as an adjunctive therapy. Techniques of massage include trigger-point massage (myotherapy or myofascial trigger-point massage), acupressure, ice massage, effleurage, petrissage, and friction or deep cross-fiber friction. In addition, passive movements as part of passive range-of-motion exercises can be classified as a form of massage because of required hands-on contact; such movements are performed within the limits of the soft tissue without stretching, and the goal is to improve synovial joint fluid production and increase joint mobility. The use and benefits of massage have been described more thoroughly in the equine, but its use in small-animal patients is increasing in popularity.

Neurologic conditions that warrant massage therapy as a potentially beneficial adjunctive treatment include head trauma and cerebrovascular accidents, spinal cord injuries such as postoperative intervertebral disk extrusion, nonsurgical fibrocartilaginous embolism (FCE), and concussive spinal cord injuries, brachial plexus injuries, and selected peripheral myopathies and neuropathies. The key to therapy is to identify the underlying disease process and to institute adjunctive massage during the recovery period. Care must be taken to choose the correct patient and the correct initiation and application of the therapy.

V. Physical Therapy^{15,16,21}

As mentioned above with massage therapy, physical therapy can be used as a beneficial adjunctive therapy in the rehabilitation process of the neurologic patient. Physical therapy involves the use of certain physical measures in the treatment and

oscillation leads to increased temperature in the tissue. Temporarily increased extensibility of the soft tissues (ligaments, tendons, and fibrous scar tissue) can occur with such heating. This accentuated flexibility, combined with range of motion exercise, can lead to clinical improvement. Ultrasound is absorbed by collagen-dense tissue; tissues with high fluid content (blood and muscle) absorb sound waves better. Nerve has a high coefficient of ultrasound absorption. Ultrasound may prove useful in treatment of peripheral nerve and muscle injuries when used appropriately.

Ultrasound is also used for its heating effects; this results from mechanical activity in the tissue as sound waves increase molecular motion. Increases in tissue temperatures cause an increase in circulation and nerve conduction velocity. Pain threshold is increased and metabolic activity is stimulated. Ultrasound can also be used to deactivate muscle trigger points and acupuncture points. Beneficial nonthermal effects of ultrasound are also theorized. Movement of the ultrasound wave through tissues produces cellular responses that aid in the stimulation of tissue repair. Fibroblasts are stimulated to produce more collagen during the granulation stage of repair, which begins about 3 days after injury. In addition, the entry of calcium ions that affect cellular activity are theorized to promote granulation. The use of therapeutic ultrasound for neurologic disease in the small animal veterinary patient is in its early stages, but it may prove useful primarily in diseases of the neuromuscular system (muscle and nerve) and may be of tremendous value in the future.

VII. Therapeutic Laser^{21,33}

Therapeutic laser (Light Amplification by Stimulated Emission of Radiation) used in veterinary medicine is gaining in popularity and is especially useful in several ways: (1) in the treatment of neurologic disorders, (2) to promote wound-healing, and (3) for cases in which there is an aversion to acupuncture needles. Traditional use includes pre- and postoperative pain management, biomodulization, soft-tissue trauma and edema, wounds, ulcers, tendinitis, and fasciitis. The most common laser types are the visible helium-neon (HeNe) lasers, invisible infrared (IR) gallium-arsenide (GaAs) lasers, and gallium-aluminum-arsenide (GaAlAs) lasers. Diode lasers are now being developed for the treatment of myofascial pain. Therapeutic lasers (Fig. 17.3) first became available in the 1970s and since 1990, 2500 articles have been listed on MEDLINE on low-level laser therapy (LLLT). Low-level laser therapy is a type of therapy that does not cause a thermal response but does cause a cellular chemical response. A more correct terminology is the term "low-energy photon therapy" (LEPT). Laser emits electromagnetic waves of 600 to 1000 nm that penetrate tissue; depth of penetration depends on tissue type and its absorption spectra. The above-mentioned lasers are designed to be used in contact with tissue and the beam is applied perpendicular to the target. Low-level laser therapy is absorbed strongly by blood proteins; if gentle pressure is applied, depth of penetration is increased. It is theorized that LEPT has both anti-inflammatory and analgesic properties; however, a correct diagnosis prior to LEPT use is mandatory. Low-energy photon therapy is also used to treat trigger points (TPs), acupuncture points (APs), and tender local points (AHSHI points), as well as painful joints, muscles, tendons,

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Chapter 18

NEUROTOXICOLOGICAL SYNDROMES

David C. Dorman

I. Introduction¹⁻⁶

This chapter focuses on common neurotoxicological syndromes that occur in companion animals. It is not comprehensive, but rather includes the diagnosis and management of common poisons that induce neurotoxicity in animals. Clinical effects (e.g., seizures) have been used to organize the presentation of the toxicants. Thus, the veterinarian can formulate reasonable differential diagnoses for suspected poisoning cases based upon observed clinical signs. However, this scheme is extremely simplistic since most neurotoxicants elicit multiple effects and the clinician may only see one phase of the clinical syndrome. In all cases, the clinician must also consider atypical presentations for a poison as well as other nontoxicological rule-outs. The chapter will also discuss clinical presentations and signs that can serve as diagnostic clues indicating that an animal displaying neurologic signs of dysfunction has been poisoned. The chapter will also address important management precautions that should be considered when treating the poisoned animal with neurologic signs.

Neurotoxicology may be broadly defined as the study of adverse effects of chemical, biological, and certain physical agents on the nervous system. In more practical terms, neurotoxicity should be considered as a disease etiology for an animal displaying neurologic signs. Neurotoxicants may act on the central nervous system (CNS), peripheral nerves, muscles, or other effector organs, and can induce structural or functional changes in the nervous system. A number of factors, including its complexity, limited capacity for repair, and high metabolic rate, predispose the nervous system to toxic insult. The nervous system is remarkably sensitive to poisons that disrupt aerobic, glucose-dependent energy metabolism and other mitochondrial functions. Elevated concentrations of polyunsaturated fatty acids and relatively low levels of antioxidant enzymes also predispose the brain to oxidative damage. The presence of myelin and other lipoproteins enhances the nervous system's susceptibility to oxidant-induced lipid peroxidation. These lipids also promote the distribution of small molecular weight, lipophilic chemicals throughout the nervous system. Most regions of the CNS can't regenerate following injury, and must compensate for neurotoxic injury. In contrast, peripheral nerves have a much higher capacity for regeneration following injury.

II. Diagnostic Considerations^{2,7-11}

Veterinary neurologists face several challenges when deciding whether or not an animal has been poisoned. The first is to verify whether the animal was exposed to a toxicant. Many different types of metals, pesticides, solvents and other chemicals,

natural toxins, and therapeutic agents may induce neurotoxicity in animals. Thus exposure can arise from a wide range of sources. Exposures may be characterized as acute or chronic with more prolonged exposures oftentimes being more difficult to establish. Second, the veterinarian should determine whether or not the exposure dose was sufficient to evoke neurotoxicity. This is especially important since neurotoxicological effects are ultimately dependent upon the exposure dose. Finally, the clinician must ascertain whether or not the observed effects are compatible with the toxicant of concern. These three factors—exposure, dose, and response—form the basis upon which a confirmed diagnosis of neurotoxicity ultimately rests.

A. Exposure history

All too often, the exposure history is inadequate or unknown, and neurotoxicity is suspected on the basis of clinical signs or other physical findings. Although tempting, a positive diagnosis should not be based upon clinical signs alone, since there are no pathognomonic signs of neurotoxicosis. Moreover, vague and seemingly unrelated clinical signs associated with many toxic syndromes may mimic disease arising from other etiologic agents (e.g., infectious agents). Despite these caveats, certain circumstances may be suggestive of poisoning. For example, the sudden onset of neurologic signs in a previously normal animal or neurologic signs in the presence of multiple-system (e.g., gastrointestinal, neuromuscular, or cardiopulmonary) involvement may suggest poisoning. In these cases, the clinician should avoid focusing solely on primary neurotoxicants since poisons that affect the liver, kidney, or other organs must also be considered in the animal demonstrating neurologic signs. For example, acetaminophen toxicosis in cats, resulting in methemoglobinemia, is often associated with CNS depression. Likewise, exposure to hepatotoxins can result in hepatoencephalopathy.

There are other ways in which the clinical presentation may provide useful diagnostic clues. For example, rapid onset, short time intervals between additional seizures, and a lack of complete recovery in the late postictal period, commonly characterize toxicant-induced seizures. Neurotoxic syndromes are often distinguished by seemingly multifocal neurologic involvement (e.g., mixed cranial nerve, peripheral nervous system, and neuromuscular involvement). Poisoning should always be suspected whenever multiple animals from the same household are displaying neurologic signs.

B. Forensic toxicology

In addition to historical and physical examination findings, other diagnostic modalities may support a diagnosis of neurotoxicosis. Chemical analysis of tissues provides an important criterion for the diagnosis of poisoning. The veterinarian should therefore collect freshly frozen postmortem tissues (e.g., liver, kidney, fat, gastrointestinal contents, and skin when dermal exposure occurred) for toxicologic analysis. The veterinarian should also collect fresh frozen brain samples (1–10 g) for chemical residue or biochemical analyses. One example is the determination of blood or brain acetylcholinesterase activity in cases of suspected poi-

soning due to cholinesterase inhibitors. The clinician must bear in mind that positive forensic findings are not always evidence of intoxication, nor do negative findings always disprove that toxicosis occurred. On occasion, neurophysiological evaluations (e.g., electroencephalography [EEG], electromyography, evoked potentials) may provide ancillary clinical evidence consistent with poisoning.

Gross and microscopic examinations will occasionally reveal valuable evidence in suspected neurotoxicologic syndromes. Samples of brain, spinal cord (e.g., cervical and lumbar intumescences), and peripheral nerves (e.g., sciatic nerve) should be collected for histopathologic examinations. Peripheral nerve tissue samples should be fixed while mildly stretched to prevent contraction artifacts. Morphologic lesions are often lacking in many neurotoxic syndromes, hence an absence of lesions can be as important diagnostically as their presence. In all cases, the careful correlation of data collected from the history, clinical and neurologic examinations, and supportive diagnostic tests is used to make a presumptive diagnosis of neurotoxicosis.

C. Information resources

The timely identification and interpretation of toxicologic information are equally important to the management of animal poisonings. With adequate information resources and interpretation of the information from these resources, most veterinarians can successfully manage the more common animal poisonings. However, there are more than 30,000 species of plants, 300,000 household products, 50,000 prescription drugs, and more than 100,000 nonprescription drugs marketed in the United States, which may lead to poisonings in small animals. Obviously, accumulation of information concerning this range of xenobiotics is beyond the capabilities of any individual veterinarian, and telephone consultation is often needed. Telephone services include human and animal poison control centers, veterinary diagnostic laboratories, and the National Pesticide Information Center (NPIC). The NPIC (1-800-858-7378; <http://npic.orst.edu>) is a cooperative effort of Oregon State University and the United States Environmental Protection Agency. The NPIC provides a toll-free telephone service that provides pesticide information to any caller in the United States, Puerto Rico, or the Virgin Islands. This service provides objective, science-based information about a wide variety of pesticide-related subjects, including pesticide products, recognition and management of pesticide poisoning, toxicology, and environmental chemistry. The NPIC is staffed by trained pesticide specialists who have education and training in toxicology and environmental chemistry.

There is one dedicated animal-oriented poison control center and more than 70 human poison control centers in the United States. The ASPCA's National Animal Poison Control Center (<http://www.napcc.asPCA.org>) provides a toxicology telephone "hotline" (900-680-0000 or 888-426-4435) that is available 24 hr a day. A consultation fee is paid by the animal owner, veterinarian, or product manufacturer. The center also provides, via fax, specific treatment protocols and current literature citations when indicated.

Both human and animal poison control centers can provide information concerning the identification of poisons, such as product formulation, trade name, generic name, scientific name (e.g., plants), or chemical name. Poison centers have access to a variety of resources, including medical libraries, reprint files, product material safety data, textbooks, manufacturers, and experts within toxicology. Most poison control centers have Poisindex (Micromedix Inc., Denver, CO), a computerized clinical toxicology information system that is frequently updated. An animal poison control center is usually a better resource for veterinarians because it is staffed by veterinarians trained in the diagnosis and management of animal poisonings. Human poison control center staff personnel are trained in the diagnosis and management of human poisonings and lack formal training and experience in veterinary medicine and veterinary toxicology.

III. Treatment Considerations¹²⁻²³

This discussion will primarily focus on management considerations for animals poisoned with a neurotoxicant. The basic strategies used in the treatment of neurotoxicosis are relatively straightforward and include (1) initiation of life support, (2) modification of the toxicokinetics of the agent to reduce its uptake or promote its elimination, and (3) antagonism of pharmacologic effects. Treatment approaches must be modified depending upon the stage of the toxic syndrome, thus repeated neurologic examinations of all animals exposed to neurotoxicants are strongly encouraged.

A. Decontamination procedures

Unless otherwise indicated, the reader should assume that the administration of an emetic (or gastric lavage) followed by activated charcoal and a saline cathartic should be used for recent oral exposures (i.e., ingestion occurred within 2 hr) to the agents discussed in this text. These decontamination procedures are used to reduce gastrointestinal absorption of the poison and thus decrease the animal's body burden of the toxicant. Emetics should **not** be given whenever potentially corrosive agents are ingested, nor to rodents or rabbits, or to animals that are hypoxic, dyspneic, extremely weak, comatose, lacking normal pharyngeal reflexes, or suffering other marked neurologic impairments that could lead to aspiration of vomitus. Additionally, if the animal has ingested a CNS stimulant, further excitement associated with vomiting may precipitate seizures. Commonly recommended emetics include syrup of ipecac (dog: 1–2 ml/kg body weight; cat: 3.3 ml/kg body weight) and 3% hydrogen peroxide (1–5 ml/kg body weight). These emetics usually induce vomiting within 5 to 15 min. If, however, an animal has not vomited by 15 min, a single repeat administration is recommended. Apomorphine and xylazine can be effective emetics for veterinary clinic use. Apomorphine can be given subconjunctivally or by intravenous or intramuscular injection. Apomorphine tablets should be dissolved in sterile water prior to subconjunctival use to limit ocular irritation. As apomorphine solutions are not stable in air or light, they must be freshly prepared before each use. Apomorphine

use is generally limited to the dog (0.03 mg/kg body weight, IV; 0.04 mg/kg body weight, IM) and may be associated with CNS depression. Xylazine (1.1 mg/kg body weight, IM or SQ) is somewhat effective as an emetic in cats. Xylazine may aggravate respiratory depression and result in vagally mediated slowing of the heart rate. The α_2 -antagonist, yohimbine (cat/dog: 0.1 mg/kg body weight, IV), has been used effectively to reverse xylazine-induced CNS depression, bradycardia, or hypotension.

Activated charcoal administration is also indicated for all cases in which significant toxicant ingestion occurred. Activated charcoal powder (1–4 g/kg body weight), combined with a saline (magnesium or sodium sulfate at 250 mg/kg body weight) or osmotic cathartic as a suspension in water (10 × volume), can be administered orally or by gastric tube. Emesis is generally favored over gastric lavage whenever the status of the patient allows for emesis to be produced. Gastric lavage is occasionally recommended, primarily for cases in which massive ingestion (more than LD₅₀) occurred, emesis is unproductive, or delayed gastrointestinal emptying is anticipated. Large-bore gastric lavage tubes and copious amounts of lavage fluid are required to perform gastric lavage adequately. Small animals generally require the use of a short-acting barbiturate or gas anesthetic before initiating gastric lavage procedures.

B. Control of seizures and CNS excitation

The clinician should use anticonvulsant therapies to control toxicant-induced seizures. Anticonvulsant therapy is discussed in detail in Chapter 6. Seizures induced by a wide range of neurotoxins are often controlled with diazepam (0.5 mg/kg IV, repeated as needed every 10 min for up to 3 doses). Diazepam may also be used for the treatment of seizures with unknown etiologies. If diazepam fails to control seizure activity, phenobarbital (6 mg/kg to effect) is typically recommended, however, a delayed onset of anticonvulsant activity often occurs. If seizures still persist, pentobarbital (slowly to effect) is often used to induce anesthesia. Placing the animal in a dark quiet room might be necessary to reduce external stimuli that may induce seizures (e.g., auditory evoked seizures associated with strychnine, bromethalin, and other neurotoxins).

Phenothiazine tranquilizers have been used to decrease excessive CNS stimulation in toxicoses arising from amphetamines or some hallucinogens (e.g., phenylcyclidine, lysergic acid diethylamide, LSD). However, this therapy has not been sufficiently reliable to gain wide acceptance. As a rule, phenothiazine tranquilizers are best avoided in poisoned animals because they may aggravate CNS depression and, in some cases, may induce extrapyramidal effects, seizures, and hypotension. Diazepam should be considered (at 2.5 to 10 mg total dose to effect, IV) when tranquilization is required (e.g., to prevent self-trauma).

C. Control of CNS or respiratory depression

Naloxone is specifically recommended for the treatment of exogenous opiate (e.g., morphine, codeine) toxicosis because it lacks opiate agonist activity. The plasma half-life and duration of action of naloxone is relatively short (45 to 90 min), thus

application of rodent toxicity data to case management requires interpretation and clinical judgment.

IV. Poisons Associated with CNS Stimulation and Seizures

Table 18.1 lists several poisons associated with CNS stimulation or seizures. Exposure to these agents may result in hyperactivity, hyperesthesia, muscle tremors and fasciculations, and behavioral manifestations (e.g., aggression). The veterinarian must be aware that head trauma may also occur secondary to toxicosis-induced ataxia and seizures. Within this chapter, seizures refer to involuntary, paroxysmal brain disturbances usually manifested by uncontrollable muscular activity (e.g., paddling), abnormal psychomotor behavior (e.g., fly biting, tail chasing), autonomic dysfunction (e.g., urination, defecation, and/or salivation), and altered behavior during the immediate postictal phase (e.g., CNS excitation or depression).

A. Amphetamine²⁴⁻²⁸

Amphetamine poisoning occurs infrequently in dogs and cats and most commonly results from the accidental ingestion of amphetamine-based stimulants. Amphetamine stimulates the release of catecholamines (e.g., norepinephrine) from the adrenal glands as well as the cerebral cortex, medullary respiratory center, and reticular activating system. Amphetamine poisoning may result in both cardiac and CNS effects similar to those induced by cocaine. Clinical effects develop within 1–2 hr after ingestion and may include hyperactivity, mydriasis,

Table 18.1: Common Neurotoxic Agents Associated with CNS Stimulation and Seizures

Aluminum Phosphide	Mercury
4-Aminopyridine (Avitrol)	Metaldehyde
Amphetamines	Methylxanthines (caffeine, chocolate)
Benzyl alcohol	<i>Narcissus</i> sp. (Daffodil, Jonquil)
Bromethalin	Opiates (cats)
Carbamate insecticides	Organochlorine insecticides (e.g., lindane)
<i>Cicuta</i> sp. (Water hemlock)	Organophosphorus insecticides
Cocaine	Piperazine
N,N-Diethyl-m-toluamide (DEET)	Pyrethrin and pyrethroid insecticides
Fluoroacetate (1080)	Strychnine
5-Fluorouracil	Tetanus toxin
Ivermectin	Thiaminase
Lead	Tremorgenic mycotoxins (e.g., penitrem)
Marijuana (rare)	Zinc phosphide

Source: Modified from Dorman DC, Diagnosis and therapy of neurotoxicological syndromes in dogs and cats, I: General concepts, *Prog Vet Neurol* 4,3: 95–103, 1993.

Note: Agents in boldface type are toxicants discussed in Chapter 18.

hyperthermia, tachycardia, lactic acidosis, hypertension, and, infrequently, seizures. The treatment of amphetamine toxicosis is primarily supportive. In addition to oral decontamination therapy, enhanced amphetamine elimination may be effected by ion trapping with urine acidification. Urine acidification is, however, contraindicated if the animal has reduced renal function or if myoglobinuria is present (e.g., secondary to muscle damage). Chlorpromazine (10 to 18 mg/kg, intravenous) or haloperidol (1 mg/kg, intravenous) given after administration of a lethal intravenous dose of amphetamine sulfate (10 mg/kg) experimentally reduced the hyperthermia severity and also increased survival rates in amphetamine-poisoned dogs. Diazepam may also be used to control seizures and may assist in calming the affected animal. Although amphetamine poisoning is rarely recognized in animals, its true incidence may be higher because of the reluctance of owners to admit to illegal drug use. The reported estimated acute oral LD₅₀ in rodents ranges from 10 to 30 mg/kg. Amphetamine may be detected in blood, cerebrospinal fluid, and other tissue samples.

B. 4-Aminopyridine (Avitrol)²⁹⁻³²

Corn baits containing 4-aminopyridine are used for the control of starlings, pigeons, and other birds. 4-Aminopyridine is highly toxic to animals with an approximate oral LD₅₀ of 3.7 mg/kg body weight in the dog. 4-Aminopyridine blocks potassium channels, resulting in increased cholinergic nervous system activity. The ability of 4-aminopyridine to block potassium channels has led to some speculation that it may be an effective therapy for multiple sclerosis. Clinical signs in poisoned animals often develop within several hours of ingestion, and commonly include tachycardia, salivation, tremors, ataxia, and seizures. Death from respiratory failure may develop within 4 hr of exposure. Chemical analysis of frozen stomach contents, liver, and urine is available at some diagnostic laboratories and residues can be detected in poisoned birds. Although no specific antidotal therapy exists, anticonvulsants and activated charcoal administration are recommended.

C. Caffeine³³⁻³⁵

The exact toxicologic mechanism of action of caffeine is not known but may include inhibition of phosphodiesterase, enhanced catecholamine release, adenosine antagonism, or increased calcium entry into the cell. Caffeine toxicosis in animals most commonly occurs following the ingestion of chocolate, however, accidental poisonings may also occur from the ingestion of caffeine-based tablets or elixirs. Caffeine is well absorbed from the gastrointestinal tract, and is nearly completely metabolized by the liver to its inactive metabolites methyluric acid and methylxanthine. The plasma half-life of caffeine in the dog is approximately 4.5 hr. Clinical signs of caffeine toxicosis in the dog and cat generally develop within several hours of ingestion and may include vomiting (often the first sign), restlessness, hyperactivity, ataxia, muscle tremors, tachycardia, cardiac arrhythmias, seizures, polyuria/polydipsia, hyperthermia, cyanosis, and coma. There are usually no histologic lesions in the brain or spinal cord. The treatment of caffeine toxicosis in animals is usually symptomatic and supportive. Fluid therapy to

of white blood cell and platelet numbers are the major hematologic abnormalities detected in dogs, occurring 2–4 days following intravenous 5-FU administration. Occasional low values of hematocrit, hemoglobin, and red cell counts also are noted following intravenous drug administrations to dogs.

Adverse CNS effects observed in 5-FU poisoned animals can include seizures, hyperesthesia, hyperexcitability, nervousness, muscle tremors, and cerebellar ataxia. Other commonly observed clinical signs include vomiting, diarrhea (occasionally bloody), pulmonary edema, respiratory failure, cardiac arrhythmias, cardiac failure, and death. The development of hyperexcitability, tremors, seizures, respiratory failure, cardiac arrhythmias, and cardiac failure (1 to 3 days postexposure) has been described in dogs following intravesicular use of 5-FU for treatment of urinary bladder transitional cell carcinoma.

Treatment of 5-FU poisoning is primarily supportive. In addition to oral or dermal decontamination, fluid therapy, anticonvulsants, antiemetics, blood transfusions, and gastrointestinal protectants are often indicated.

F. Lead^{50–76}

The incidence of lead toxicosis in companion animals appears to be decreasing; nevertheless, it remains an important clinical problem. Sources of lead include lead-based paints, battery plates, certain caulking compounds and putty, linoleum, plumbing solder, roofing material, and asphalt. Water from lead plumbing, glazed crockery pots, and streams polluted by lead-contaminated effluent also may contain toxic concentrations of lead. Young animals are more susceptible to lead poisoning than are adults, and poisoning is more common in dogs than in cats.

The most common route of exposure to lead is via ingestion. Generally, only 5 to 10% of ingested lead is absorbed in adults, but 40 to 50% is absorbed from the gastrointestinal tract in juveniles. Lead may dissolve to an appreciable degree in the acid environment of the stomach, greatly increasing its absorption. In contrast, metallic lead shots or bullets lodged in tissue do not readily dissolve except in joints or abscesses. Once absorbed, lead readily passes membrane barriers such as the blood-brain barrier and the placenta. Distribution is primarily to the kidney cortex, liver, and bone; the bone contains up to 90 to 98% of the total body lead burden. When the bone becomes saturated, signs of toxicosis may develop suddenly.

Signs of lead toxicosis are generally referable to the nervous and gastrointestinal systems. Neurologic signs with acute onset tend to predominate with higher exposure levels, while gastrointestinal signs and chronic illness may be more common with lower exposures; however, both systems may be affected concurrently. In decreasing order of frequency, clinical signs of lead toxicosis in dogs and cats are vomiting, seizures, anorexia, hysteria, and weight loss. In both dogs and cats, seizures are the predominant neurologic sign; therefore, lead toxicosis should be considered in any animal exhibiting seizures. EEG changes in dogs with lead-induced neurologic signs include intermittent or continuous high-amplitude slow wave activity. Hysteria is also commonly reported and is characterized by barking

and crying continuously, running in many directions without purpose, indiscriminate biting of animate and inanimate objects, and other behavioral changes. Other neurologic signs include ataxia, tremors, and blindness. Dogs may also develop aggression, dementia, pica, megaesophagus, and coma. Cats tend to show more evident neurologic manifestations and less prominent gastrointestinal signs than dogs. Megaesophagus attributable to lead toxicosis has also been reported in cats. Differential diagnoses based upon history and clinical signs include rabies, canine distemper, epilepsy, encephalitis, spinal cord trauma, and other poisons.

Blood lead determinations are the single best indicator of exposure to lead. Whole blood (heparinized or EDTA-containing tubes) rather than serum should be used because 90% of circulating lead is bound to erythrocytes. Although a valuable indicator of exposure, blood lead concentrations do not reflect the length of exposure or total body burden amount of lead. Also, blood lead concentrations may not correlate well with the severity of clinical signs. Signs of toxicosis may resolve fairly quickly following the initiation of therapy, despite concurrent high blood lead concentrations. Cats may exhibit signs of lead toxicosis at lower blood lead concentrations than dogs. The finding of numerous erythrocytes with basophilic stippling and/or immature (especially nucleated) erythrocytes without evidence of anemia is suggestive of lead poisoning in the dog. Other causes of nucleated red blood cells (e.g., endotoxemia, leukemia, splenic diseases) should also be considered. Lead inhibits the serum enzyme delta aminolevulinic acid (ALA) dehydratase, resulting in a measurable increase in the elimination of ALA in the urine of lead-poisoned dogs and cats. Determination of ALA urinary excretion has some merit as a diagnostic test for lead poisoning; however, urinary ALA may be unreliable when the daily intake of lead is small (e.g., chronic intake). Lead also inhibits ferrochelatase, an enzyme in the heme biosynthetic pathway. This results in accumulation of protoporphyrin in the red blood cells of lead-poisoned animals and can be used as a highly sensitive test for exposure to lead. Paint chips or other lead objects within the gastrointestinal tract may occasionally be detected on abdominal radiographs. Radiopaque material in the gastrointestinal tract helps to rule in lead toxicity, but negative findings do not rule it out.

For postmortem diagnosis, fresh frozen liver and kidney tissue should be submitted for lead chemical assay. Histologic changes potentially induced by lead include renal tubular necrosis and amorphous acid-fast intranuclear inclusions in hepatocytes and renal tubular epithelial cells. Lesions occur in the CNS (lead encephalopathy) as well as in the peripheral nervous system (lead neuropathy). The likely primary lesion in acute human lead encephalopathy is breakdown of the blood-brain barrier and similar effects are also observed in animals. Brain capillaries may be dilated, narrowed, necrotic, or thrombosed, and endothelial cells often swell. The consequent extravasation of fluid results in cerebral and cerebellar edema. Accompanying these vascular changes are neuronal necrosis (cerebrocortical and Purkinje cells) with secondary reactive gliosis and astrocytic scar formation. Neuronal lesions may be caused directly by lead rather than by defective vascular function since neuronal necrosis without vascular injury has been observed in acute experimental lead toxicity. In the PNS, lead neuropathy in

humans and experimental animals is manifested by Wallerian axonal degeneration and segmental demyelination affecting primarily motor nerves.

Treatment of lead poisoning is directed at controlling seizures and other life-threatening signs; removing lead from the gastrointestinal tract; elimination of absorbed lead from soft tissue and bone; and identifying the source in order to prevent further exposure. Small pieces of metallic lead and lead paint chips can be removed from the gastrointestinal tract with emetics and saline cathartics. Larger lead objects in the stomach or intestine may require endoscopic or surgical removal.

Historically, the most commonly used chelator for lead has been CaNa_2EDTA . This agent has been used in a variety of animal species. In both cats and dogs, CaNa_2EDTA is given subcutaneously at 18.75 to 27.5 mg/kg, every 6 hr, for 2 to 5 days. Prior to injection, CaNa_2EDTA should be diluted to a final concentration of 10 mg/ml in 5% dextrose solution. Higher concentrations of CaNa_2EDTA may cause pain at the injection site. Intravenous injection may be more effective, but requires additional labor resources. Continuous CaNa_2EDTA therapy should not last more than 5 days because of CaNa_2EDTA 's effects on normal growth of the intestinal epithelium, enhanced zinc elimination, and nephrotoxicity; however, multiple treatments are occasionally necessary and each 5 days of treatment should be followed by a 5-day rest period. The clinical condition of the animal and blood lead measurements are used to determine when to stop therapy. Due to CaNa_2EDTA -induced increases in zinc elimination, oral zinc supplementation at 2 mg/kg may be necessary in dogs on low-zinc diets or those given multiple chelation treatments.

D-Penicillamine has also been recommended for asymptomatic dogs as a home-based follow-up therapy to inpatient chelation therapy, especially in animals with persistently elevated blood lead concentrations. D-Penicillamine is given orally at 110 mg/kg daily for 2 wk followed by a 1-wk rest. To prevent chelation of essential metals in the diet, D-Penicillamine should be administered on an empty stomach (30 min before feeding). It may be necessary to divide the daily dose and give it every 6 to 8 hr or decrease the total dose to 33 to 55 mg/kg daily if adverse effects such as vomiting, listlessness, or anorexia persist. Antiemetic drugs may also be administered 30 min to 1 hr before the D-penicillamine to reduce vomiting. D-Penicillamine is a well-absorbed oral chelation agent used for the treatment of lead and mercury toxicosis. D-Penicillamine is metabolized by the liver with very little excreted unchanged, and elimination is primarily via the kidney and liver. Side effects associated with D-Penicillamine use include reversible proteinuria and hematuria. It may also enhance the absorption of lead from the gastrointestinal tract; therefore, gastrointestinal tract decontamination prior to chelation therapy and prevention of further exposure to lead are important.

The use of 2, 3-dimercaptosuccinic acid (DMSA; Succimer) has dramatically improved lead chelation therapy. In contrast to other chelators, DMSA is a relatively selective, orally active, water-soluble chelating agent. A hydrophilic, less-toxic analog of British Anti-Lewisite (BAL), DMSA is used for the treatment of

lead, arsenic, and organic mercury toxicosis. In contrast to the enhanced intestinal absorption of lead induced by D-Penicillamine, orally administered DMSA apparently does not increase intestinal lead absorption, and potentially may reduce it. It is still imperative to prevent ongoing oral exposure to lead; however, if reexposure should occur (as in an outpatient setting), concurrent treatment with DMSA is unlikely to pose a particular risk. Side effects of DMSA are limited. Elevations in serum alanine transaminase have been reported in humans, but these also may be induced by lead toxicosis. DMSA appears not to have a clinically significant effect on the excretion of essential minerals including calcium, magnesium, iron, copper, and zinc. Dogs treated with DMSA (10 mg/kg body weight, per os, every 8 hr) for 10 days had reduced blood lead concentrations and eliminated clinical signs of lead poisoning. Succimer has also been used effectively in cats poisoned with lead. Thiamine hydrochloride (2 mg/kg body weight, every 6 hr) may be beneficial in lead-poisoned dogs, although its efficacy has not been proven experimentally.

Another factor that should be considered is the possibility that children or adults may also have been exposed to lead from the same source as their pets. This is especially true if the exposure history includes possible risk factors for exposure like a recent remodeling of an older home that contains lead-based paints.

G. Lindane and other organochlorine insecticides⁷⁷⁻⁸¹

Animal exposures to organochlorine insecticides (e.g., lindane, endrin, DDT) continue to result in serious neurotoxicoses. Endrin has been used as an avicide, and toxicosis in the cat can result from secondary poisoning from ingestion of endrin-poisoned birds. Of the organochlorine insecticides, lindane is of most toxicologic significance in companion animals. Lindane toxicosis is most commonly the result of the overuse of lindane-based insecticides on dogs or its inappropriate use on cats. Since lindane use has been curtailed, the incidence of lindane poisoning appears to be waning. The minimal oral lethal dose for lindane in most mammalian species ranges from 5 to 50 mg/kg body weight.

Lindane is a DDT-type organochlorine insecticide, and acts by causing partial depolarization by inhibiting normal sodium and potassium ion channel function. Lindane may also affect the gamma amino butyric acid (GABA)-receptor-ionophore complex. As lindane and other organochlorine insecticides are very lipophilic, they are rapidly absorbed and tend to develop high fat and brain tissue concentrations. Clinical signs of lindane toxicosis generally develop within 24 hr of exposure. Signs may be progressive or explosive in nature, and commonly include CNS excitation, tremors, clonic-tonic seizures, hyperactivity, ataxia, circling, salivation, hyperthermia, and coma. Liver damage is occasionally observed several days after exposure. EEG changes in lindane-poisoned humans can include increased low amplitude-fast frequency and spike activities. Treatment of toxicosis is largely supportive (washing skin, gastrointestinal tract decontamination, seizure control, fluids, oxygen, and respiration support).

H. Penitrems⁸²⁻⁸⁶

Tremorgens are mycotoxins (secondary fungal metabolites) that contain an indole moiety, presumably derived from tryptophan, that produce tremors or seizures in animals consuming toxic amounts of contaminated foodstuffs. There are five groups of tremorgens: penitrems, paspalitrems, fumitremorgins, verruculogens, and tryptoquivalines. Each of these mycotoxins has been associated with animal poisoning; however, the penitrems are the most important class for companion animals. Sources of penitrem A include moldy refrigerated foods, cottage cheese, cream cheese, walnuts, peanuts, and other stored grains and mixed feeds.

Although the mechanism(s) of action of penitrems is incompletely understood, known biochemical effects include alterations in the resting potential, end-plate potential, and duration of depolarization of the nerve cell. Penitrem A also has been shown to facilitate transmission of impulses across the motor end plate by altering presynaptic transmitter release. It has also been suggested that penitrem A inhibits the inhibitory neurotransmitter glycine. The acute oral LD₅₀ for penitrem A and B in rodents are 1.05 and 5.84 mg/kg body weight, respectively. Clinical signs of penitrem poisoning in animals include tremors, seizures, prostration, and polyuria. Dogs will often demonstrate severe muscle tremors and intermittent seizure episodes for several hours after the onset of clinical signs. Affected animals will gradually return to normal over 1–2 days. Some diagnostic laboratories have developed methods to detect penitrem A in biological samples using thin-layer chromatography (TLC) or mass spectrometry methods. No specific lesions are anticipated to be seen at necropsy or on histopathology. Secondary trauma is possible as the result of seizures. Drugs that increase glycine in the CNS including mephenesin or nalorphine have been shown to abolish penitrem A tremors in mice; however, the efficacy and safety of these treatments in companion animals has not been investigated. Treatment of toxicosis is therefore largely supportive (gastrointestinal tract decontamination, seizure control, fluids, oxygen, and respiration support).

I. Pyrethrin and pyrethroid insecticides⁸⁷⁻⁹³

Pyrethrins are natural insecticides, while pyrethroids (e.g., permethrin and fenvalerate) are more stable synthetic insecticides. Toxicologic mechanisms of action of these insecticides include interference with sodium channels, enhanced sodium ion conductance, and post-synaptic GABA receptor-chloride ionophore complex blockade. Pyrethrins and pyrethroids possess low acute oral toxicity to mammals (acute oral LD₅₀s range from 25 to 10,000 mg/kg body weight) due to their rapid hydrolysis in the gastrointestinal tract and liver metabolism. Synergists (e.g., piperonyl butoxide, and N-octyl-bicycloheptene dicarboximide [MGK 264]) are generally used to decrease pyrethrin and pyrethroid metabolism and increase their insecticidal activity. It is likely that esterases involved in pyrethrin and pyrethroid insecticide metabolism may also be inhibited by prior organophosphorus or carbamate insecticide exposure, increasing the likelihood of pyrethrin toxicosis.

Toxicosis generally develops within hours of exposure, but may be delayed as a result of prolonged exposure from dermal absorption or grooming. Clinical

signs associated with the development of pyrethrin or pyrethroid insecticide poisoning in cats and dogs include tremors, increased salivation, ataxia, vomiting, CNS depression, hyperexcitability or hyperactivity, seizures, dyspnea, and death. The toxic syndrome is considered reversible in most sublethally exposed animals with complete recovery occurring within 72 hr. Gross or microscopic lesions are typically absent. Chemical analysis for insecticide residues on the skin or in the gastrointestinal tract of exposed animals may be used to confirm topical or oral exposure to these agents. Elevated tissue concentrations of these insecticides, especially brain and fat, may also help to support a tentative diagnosis of lethal poisoning. Direct correlation between tissue concentrations and severity of clinical signs (including death) for most insecticides have not been determined for cats or dogs. Treatment of toxicosis is largely supportive (washing skin, gastrointestinal tract decontamination, seizure control, fluids, oxygen, and respiratory support). Atropine (0.04 mg/kg, SQ) may diminish the degree of salivation and diarrhea in pyrethrin- or pyrethroid-poisoned cats. Unlike its use in organophosphorus or carbamate insecticide toxicosis, however, atropine is not considered a direct antidotal therapy for pyrethrin or pyrethroid insecticide poisoning.

J. Strychnine^{62,94-99}

Strychnine acts by competitively and reversibly antagonizing the inhibitory neurotransmitter glycine at postsynaptic sites in the spinal cord and medulla. Inhibition of glycine results in the development of muscle tremors, hyperesthesia, seizures, opisthotonus, tetany (sawhorse stance), and extensor rigidity. Clinical signs usually appear within 10 min to 2 hr following ingestion of the poison. All domesticated species are sensitive to this highly toxic agent with approximate lethal doses ranging from 0.5 to 5.0 mg/kg body weight. Initially the patient may appear apprehensive, nervous, tense, and stiff. The clinical signs observed during strychnine poisoning (e.g., tetany, "sardonic grin," sawhorse stance, seizures, opisthotonus) closely resemble those resulting from tetanus. Unlike tetanus, strychnine induces a rapidly progressive syndrome. With time, intermittent periods of relaxation become progressively shorter until status epilepticus develops. Violent tetanic seizures may appear spontaneously, or alternatively, a variety of stimuli (e.g., touch, sound, or bright lights) can initiate seizures. Death eventually results secondarily to anoxia during the tetanic seizures or exhaustion. The entire syndrome, if left untreated, may last 1 to 2 hr before death ensues. Gross or microscopic lesions are typically absent in strychnine toxicoses.

Effective control of seizures is critical to the management of strychnine poisoning. Along with anticonvulsant therapy, glyceryl guaiacolate (5%, 110 mg/kg body weight, IV) or methocarbamol (150 mg/kg body weight, IV) may be of benefit in strychnine toxicosis. Two to five or more doses of glyceryl guaiacolate should be given at intervals ranging from 20 min to 6 hr. The time between treatments and the number of treatments are based on the clinical condition of the animal. The muscle relaxant methocarbamol has also been used to control strychnine-induced seizures in dogs for 30 min to 2 hr. Tachycardia and vasopressor effects associated with strychnine can be treated with diazepam (0.1 to 0.2 mg/kg

body weight, IV), phentolamine (0.5 mg/kg body weight, IV), and propranolol (0.5 to 1.0 mg/kg body weight, IV).

Once the animal's condition has been stabilized, and the seizures are under control, gastrointestinal decontamination with activated charcoal is performed. Strychnine elimination can also be enhanced by forced diuresis (5% mannitol in 0.9% sodium chloride administered at the rate of 6.6 ml/kg/hour) and acidification of the urine with ammonium chloride (132 mg/kg body weight, PO).

Unfortunately, in many cases forced diuresis with acidification has minimal benefit. Urine acidification is contraindicated if exertional acidosis, myoglobinuria, or metabolic acidosis is present. With proper management, clinical signs resulting from the ingestion of this rodenticide generally resolve within 24 hr. Some diagnostic laboratories have developed methods to detect strychnine in biological samples using thin-layer chromatography (TLC) or mass spectrometry methods. The use of strychnine has been greatly reduced and companion animal poisoning has become relatively rare.

K. Sodium fluoroacetate (compound 1080)¹⁰⁰⁻¹⁰³

Sodium fluoroacetate (compound 1080) induces an acute (signs develop within 30 to 90 min after ingestion) syndrome similar to strychnine poisoning. Fluoroacetate undergoes metabolism to fluorocitrate, a potent inhibitor of the Krebs cycle enzyme, aconitase. In dogs, fluoroacetate primarily affects the CNS, while in cats it also results in cardiotoxicity. In addition to tremors and seizures, vomiting, diarrhea, urination, vocalization, and "running fits" also commonly develop following ingestion of a lethal dose (~ 0.05 mg/kg body weight). Episodes of wild running and barking are interrupted by tonic-clonic seizures, opisthotonus, and paddling. Cats also develop hyperesthesia, salivation, vocalization, muscle tremors, and seizures. Death from respiratory failure typically ensues within 2 to 12 hr after the onset of signs. Gross or microscopic lesions are typically absent in sodium fluoroacetate toxicoses. Although no specific antidotal therapy exists, anticonvulsants and activated charcoal administration are recommended. Fortunately, the use of sodium fluoroacetate is under tight regulatory control in the United States and companion animal poisoning from the rodenticide has become extremely rare.

V. Toxicants Causing Paralysis

Ataxia, paresis, and paralysis are gait alterations associated with dysfunction of the central or peripheral nervous system. Ataxia is defined as a failure of muscle coordination, paresis as a partial loss or impairment of motor function, and paralysis as complete loss or impairment of motor function in a body part. The reader is referred to Table 18.2 for possible differential diagnoses. Some of these agents may also result in respiratory paralysis (e.g., aminoglycoside antibiotics).

Hexachlorophene-induced toxicosis¹⁰⁴⁻¹⁰⁸ has been reported in dogs and cats following its overzealous dermal use or from accidental ingestion of hexachlorophene-

Table 18.3 Common Neurotoxic Agents Associated with CNS Depression, Stupor, or Coma

Barbiturates	Levamisole
Benzodiazepines	d-Limonene
Benzyl alcohol	Mercury
Bromethalin	Metaldehyde
<i>Cannabis sativa</i> (marijuana)	Methionine
Carbamate insecticides	Opiates (e.g., morphine)
Citrus oil extracts	Organophosphorus insecticides
N,N-diethyl-m-toluamide (DEET)	Phenothiazine tranquilizers
Ethanol	Piperazine
Ethylene glycol	Pyrethrin and pyrethroid insecticides
Ivermectin	Thiaminase
Lead	Zinc phosphide

Source: Modified from Dorman DC, Diagnosis and therapy of neurotoxicological syndromes in dogs and cats, I: General concepts, *Prog Vet Neurol* 4,3: 95–103, 1993.

Note: Agents in boldface type are toxicants discussed in Chapter 18.

responds to painful stimuli. In coma, animals are unconscious and unresponsive to any stimulation. The presence of CNS depression alone is not useful diagnostically since it often occurs in any ill or intoxicated animal. Agents that induce CNS depression may also inhibit cardiopulmonary function resulting in hypotension, respiratory depression, and secondary cerebral hypoxia.

A. Barbiturates^{38,109–112}

Barbiturate use in human medicine has decreased significantly in recent years, while barbiturates are still widely used in veterinary medicine. Animal poisoning may be the result of the ingestion of barbiturate-based drugs, ingestion of barbiturate euthanized animals, ingestion of illicit street preparations, or from iatrogenic overdose. Barbiturates have multiple mechanisms of action including inhibiting calcium accumulation in neural tissue, inhibition of neurotransmitter release, and GABA-mimetic action within the CNS. Profound respiratory and CNS depression, general anesthesia, hypothermia, hypotension, shock, cyanosis, and coma are the predominant clinical signs observed following barbiturate exposure. Death is usually caused by respiratory arrest.

Barbiturates are commonly classified according to their duration of effect into long, intermediate, short, or ultrashort acting. In general, barbiturates are rapidly distributed throughout the body, although their distribution is influenced by the lipid solubility of the individual agent. Dependent on species and chemical form, barbiturates are metabolized extensively by the hepatic microsomal enzyme system and are also eliminated by renal excretion. Nonhepatic metabolism (kidney, brain, and other tissues) may also contribute to the metabolism of some barbiturates.

Termination of biologic activity is by redistribution in the body and side-chain oxidation. Substantial amounts of phenobarbital are excreted unchanged by

the kidney in a pH-dependent process. Treatment of barbiturate poisoning involves gastrointestinal tract decontamination (e.g., emetics, repeated administration of activated charcoal, gastric lavage) and the initiation of life-supportive measures (e.g., ventilatory support, fluid therapy). Forced alkaline diuresis may also be of benefit in phenobarbital toxicoses. Hemodialysis and hemoperfusion are also employed in severely affected human patients. Redistribution of these drugs from adipose tissue back to the plasma may cause continued CNS depression, therefore, repeated patient monitoring is required.

B. Ivermectin^{113–126}

Ivermectin is a naturally occurring combination of the polycyclic lactones 22,23-dihydro avermectin β 1a and β 1b. Ivermectin is used as an anthelmintic in cattle, horses, and swine, and has been approved for the prevention of canine heartworm infection (6 μ g/kg body weight, monthly). Ivermectin toxicosis in dogs and cats often follows the inappropriate administration of ivermectin-based equine anthelmintic by the animal's owner.

Ivermectin neurotoxicity is related to its agonist effects at the GABA-chloride channel. The normally inhibitory neurotransmitter, GABA, is found in the CNS of mammals (cerebellum, cerebral and limbic cortices, extrapyramidal system, and horizontal layer of the retina), whereas GABA acts peripherally in invertebrates. Ivermectin potentiates synaptic GABA effects by enhancing its presynaptic release and by enhancing the binding of GABA to its postsynaptic receptors. In general, p-glycoproteins found within the blood-brain barrier of mammals prevent ivermectin from entering the brain. Mice that lack this barrier function are more sensitive to the neurotoxic effects of ivermectin. Some Collies, Shelties, and Border collies are also at increased risk for ivermectin toxicity; however, it is unknown whether these animals have a decrease in p-glycoprotein expression in their blood-brain barrier.

Although some individuals are extremely sensitive, any member of a breed or species could become poisoned with ivermectin if an extremely high exposure were to occur. Ivermectin poisoning typically results in an acute (within 4–6 hr after ingestion) onset of ataxia, muscle tremors, seizures (rarely observed), disorientation, mild to severe CNS depression, and sometimes coma, which may be prolonged or proceed to cause death. Some dogs develop mydriasis, decreased menace response, and apparent blindness, which with time is reversible. Vomiting, diarrhea, hyperthermia, bradycardia, and sinus arrhythmia have also been reported. There are no characteristic pathologic lesions in ivermectin-poisoned animals.

Ivermectin is poorly absorbed from the gastrointestinal tract and undergoes limited hepatic metabolism. Peak plasma concentrations are reached within 3 hr after oral administration, and the plasma half-life in noncollie breed dogs has been reported to be 2 to 3 days. Ivermectin has a wide oral margin of safety, yet it has been reported to be neurotoxic in some (but not all) Collies, Old English sheepdogs, and other susceptible breeds following single oral doses of approximately 100 to 500 μ g/kg body weight.

diazepam. Atropine may be given for bradycardia, excessive bronchoconstriction, or diarrhea. Assisted pulmonary ventilation may be necessary for the management of respiratory paralysis.

B. Organophosphorus and carbamate insecticides^{78,93,140-145}

Organophosphorus (OP) and carbamate insecticides are potent inhibitors of acetylcholinesterase and produce muscarinic (salivation, lacrimation, bronchial secretion, vomiting, diarrhea), nicotinic (tremors, respiratory paralysis), and CNS (seizures, miosis, hyperactivity) effects. Carbamate insecticides are reversible acetylcholinesterase inhibitors while organophosphorus insecticides bind covalently to the enzyme, resulting in irreversible inhibition of the enzyme. Recovery following exposure to an OP insecticide is therefore dependent upon the resynthesis of acetylcholinesterase. Tolerance to some cholinergic effects of cholinesterase-inhibiting compounds may be due to compensatory down-regulation of muscarinic receptors. Poisonings from OP (e.g., chlorpyrifos, dichlorvos) and carbamate (e.g., aldicarb, methomyl, carbofuran) insecticides are commonly the result of deliberate topical application or accidental ingestion.

Measurement of whole blood, brain, or retinal acetylcholinesterase activity is diagnostically useful in cases in which an exposure to an OP or carbamate insecticide may have occurred. Depending on the diagnostic laboratory's preference, whole blood samples (collected in the appropriate anticoagulant), serum, plasma, and retinal or brain tissue (one hemisphere) should be frozen and shipped on ice. The presence of reduced acetylcholinesterase activity (less than 50% normal activity) in blood, brain, or retinal tissues is supportive of a diagnosis of OP or carbamate insecticide toxicosis. In contrast to OP insecticides, transient inhibition by carbamate insecticides makes assessment of acetylcholinesterase activity more difficult, since acetylcholinesterase activity may be reactivated spontaneously *in vivo*, during tissue shipment, following incubation (as occurs with some methods of measuring acetylcholinesterase activity), or during storage. In contrast, cholinesterase activity in tissues from organophosphorus insecticide poisoned animals are not altered by incubation.

Important differences exist between dog and cat cholinesterase activity. Feline whole blood cholinesterase activity is composed primarily of a pseudocholinesterase (butyrylcholinesterase) that is extremely sensitive to inhibition by OP insecticides. A significant decrease in whole blood acetylcholinesterase activity is, therefore, anticipated in a clinically affected cat suspected of being poisoned with an OP insecticide. However, reduced blood cholinesterase activity may also occur in exposed cats that are not clinically affected. Therefore, the prognostic value of this test is difficult to assess. Furthermore, significant inhibition of brain cholinesterase activity may occur in cats and dogs with normal blood cholinesterase activity (i.e., false negative).

One example of an organophosphorus insecticide of concern in veterinary medicine is chlorpyrifos. Chlorpyrifos is marketed under the trade names Dursban and Lorsban and is used for the control of termites, corn rootworm, cattle

parasites, and fleas. Animal formulations available for the control of fleas include dips, sprays (polymer-based), and collars. However, except for flea collars, chlorpyrifos has not been approved for use on cats. The inappropriate use of chlorpyrifos-based products on cats or in their environment results in a significant number of toxicosis cases each year. The minimal lethal dose of chlorpyrifos in the cat is between 10 and 40 mg/kg body weight. Some cats may develop severe clinical signs following exposures to even smaller doses, especially if chronically exposed.

Clinical signs of chlorpyrifos toxicosis in the cat often persist for weeks, during which time the patient may become progressively debilitated. This prolonged clinical syndrome may be related to persistent absorption of chlorpyrifos from the skin of topically exposed cats. Although not specific for chlorpyrifos toxicosis, electromyographic (EMG) abnormalities reported to occur in chlorpyrifos-poisoned cats include prolonged insertion activity, fibrillation potentials, positive sharp waves, and high-frequency discharges consistent with a neuropathy or neuromyopathy. Electromyographic changes are most severe in the pelvic limbs. Elevation of serum creatine kinase activity has also been reported in chlorpyrifos-poisoned cats.

Chlorpyrifos exposure in cats has been associated with the development of organophosphate-induced delayed neuropathy (OPIDN). The ability of chlorpyrifos to produce OPIDN is not related to acetylcholinesterase inhibition. Although controversial, the postulated mechanism of action in the development of OPIDN involves the phosphorylation and aging of a second class of esterase, neuropathy target esterase (NTE). In the cat, this neuropathy is characterized by a central-peripheral distal axonopathy ("dying-back polyneuropathy"). The appearance of clinical signs is delayed for up to 2 to 3 wk after exposure. This syndrome is rarely encountered clinically, but when it occurs it is characterized by ataxia, pelvic-limb hypermetria, depressed conscious proprioception, weakness, and an ascending paralysis. The list of differential diagnoses for chlorpyrifos toxicosis should include thiamine deficiency, hypokalemia, and viral, bacterial, or fungal meningoencephalitis. Other OP and carbamate insecticides, pyrethrin, pyrethroid, and organochlorine insecticides, and other seizure- or tremor-producing neurotoxins should also be considered.

Treatment of OP or carbamate insecticide-poisoned animals should begin with institution of life-saving symptomatic therapy. Atropine sulfate (0.1–0.2 mg/kg body weight, repeat as needed) can be used to alleviate respiratory distress caused by severe bradycardia and excessive bronchiolar constriction and hypersecretion. Atropine will not, however, abolish the muscle tremors and other signs due to excessive nicotinic stimulation. The initial dose of atropine should be divided, with one-quarter given intravenously and the remainder given either subcutaneously or intramuscularly. Since long-term atropine therapy may be required, one should use the lowest dose that alleviates the dyspnea and bradycardia. The reversal of excessive salivation may serve as a useful clinical marker of effective atropinization, however, pupil size is an unreliable indicator of atropinization in cats and dogs. The dose of atropine should be decreased or dis-

tion. Treatment of toxicosis is largely supportive (gastrointestinal tract decontamination, seizure control, fluids, oxygen, and respiratory support).

VIII. Neurotoxic Chemicals with Mixed Effects on the CNS

Table 18.5 includes toxicants that produce a combination of nervous system clinical signs. Many of these agents may produce either CNS stimulation or depression depending upon the exposure dose, the species of animal involved, and the stage of the toxic syndrome. Some of these agents also attack multiple sites within the nervous system, leading to mixed clinical effects and signs. Some neurotoxicants with mixed effects will also impair sensory function.

A. Bromethalin¹⁴⁸⁻¹⁵⁷

Rodenticides containing 0.01% bromethalin (N-methyl-2,4-dinitro-N-[2,4,6-tri-bromophenyl]-6-[trifluoromethyl] benzeneamine) have been marketed since 1985. Bromethalin and its primary N-demethylated metabolite, desmethyl-bromethalin, are effective uncouplers of oxidative phosphorylation. Uncoupling of oxidative phosphorylation results in inadequate adenosine triphosphate synthesis leading to decreased sodium and potassium ion channel pump activity. This, in turn, leads to cerebral edema and elevated cerebrospinal fluid pressure. The reported minimal lethal dose in the cat is 0.45 mg/kg body weight, with the dog being approximately five- to sixfold less sensitive. Secondary poisoning of cats through the ingestion of bromethalin-poisoned rodents may occur. The onset and severity of clinical signs induced by bromethalin are dose-dependent.

Ingestion of extremely high doses of bromethalin (more than LD₅₀) may result in an acute onset of CNS excitation, muscle tremors, and seizures.

Bromethalin ingestion by dogs and cats, however, more commonly occurs at

Table 18.5: Common Neurotoxic Agents with Mixed Effects on the CNS

Boric acid	Methionine
Bromethalin	Metoclopramide
Carbon disulfide	Metronidazole
Chlorhexidine	Phenothiazine tranquilizers
N,N-diethyl-m-toluamide (DEET)	Pyrethrin and pyrethroid insecticides
Ethylene glycol	<i>Pyriminil</i> (Vacor)
Hexachlorophene	Rotenone
Lead	Toluene
LSD	Tricyclic antidepressants
Mercury	Zinc phosphide

Source: Modified from Dorman DC, Diagnosis and therapy of neurotoxicological syndromes in dogs and cats, I: General concepts, *Prog Vet Neurol* 4,3: 95-103, 1993.

Note: Agents in boldface type are toxicants discussed in Chapter 18.

phosphide to phosphine is retarded by gastric lavage with an aluminum or magnesium hydroxide gel (e.g., Maalox).

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A Practical Guide to **CANINE AND FELINE NEUROLOGY**

Although a working knowledge of neuroanatomy is necessary for clinicians, learning neuroanatomy in depth is rarely an achievable goal of any practicing veterinarian. *A Practical Guide to Canine and Feline Neurology* is a succinct handbook of canine and feline clinical neurology. It provides the necessary tools to understand and be clinically proficient with neurology cases faced in small-animal practice.

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A Practical Guide to Canine and Feline Neurology is an excellent reference source for general small-animal practitioners, veterinary students, interns, residents, specialists, and anyone needing a refresher course on neurology before taking specialty board or state board examinations.

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